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(54) Title: COMPOSITIONS AND METHODS RELATING TO BREAST SPECIFIC GENES AND PROTEINS

(57) Abstract: The present invention relates to newly identified nucleic acids and polypeptides present in normal and neoplastic breast cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions comprising the nucleic acids, polypeptides, antibodies, variants, derivatives, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and non-cancerous disease states in breast tissue, identifying breast tissue, monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered breast tissue for treatment and research.

COMPOSITIONS AND METHODS RELATING TO BREAST SPECIFIC GENES AND PROTEINS

This application claims the benefit of priority from U.S. Provisional Application
5 Serial No. 60/252,509 filed November 22, 2000, which is herein incorporated by
reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to newly identified nucleic acid molecules and
10 polypeptides present in normal and neoplastic breast cells, including fragments, variants
and derivatives of the nucleic acids and polypeptides. The present invention also relates
to antibodies to the polypeptides of the invention, as well as agonists and antagonists of
the polypeptides of the invention. The invention also relates to compositions comprising
the nucleic acids, polypeptides, antibodies, variants, derivatives, agonists and antagonists
15 of the invention and methods for the use of these compositions. These uses include
identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and non-
cancerous disease states in breast tissue, identifying breast tissue and monitoring and
identifying and/or designing agonists and antagonists of polypeptides of the invention.
The uses also include gene therapy, production of transgenic animals and cells, and
20 production of engineered breast tissue for treatment and research.

BACKGROUND OF THE INVENTION

Excluding skin cancer, breast cancer, also called mammary tumor, is the most
common cancer among women, accounting for a third of the cancers diagnosed in the
United States. One in nine women will develop breast cancer in her lifetime and about
25 192,000 new cases of breast cancer are diagnosed annually with about 42,000 deaths.
Bever, *Primary Prevention of Breast Cancer*, in *BREAST CANCER*, 20-54 (Kelly K Hunt
et al., ed., 2001); Kochanek et al., 49 Nat'l. Vital Statistics Reports 1, 14 (2001).

In the treatment of breast cancer, there is considerable emphasis on detection and
risk assessment because early and accurate staging of breast cancer has a significant
30 impact on survival. For example, breast cancer detected at an early stage (stage T0,
discussed below) has a five-year survival rate of 92%. Conversely, if the cancer is not

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detected until a late stage (i.e., stage T4), the five-year survival rate is reduced to 13%.
AJCC Cancer Staging Handbook pp. 164-65 (Irvin D. Fleming et al. eds., 5th ed. 1998).
Some detection techniques, such as mammography and biopsy, involve increased
discomfort, expense, and/or radiation, and are only prescribed only to patients with an
5 increased risk of breast cancer.

Current methods for predicting or detecting breast cancer risk are not optimal.
One method for predicting the relative risk of breast cancer is by examining a patient's
risk factors and pursuing aggressive diagnostic and treatment regimens for high risk
patients. A patient's risk of breast cancer has been positively associated with increasing
10 age, nulliparity, family history of breast cancer, personal history of breast cancer, early
menarche, late menopause, late age of first full term pregnancy, prior proliferative breast
disease, irradiation of the breast at an early age and a personal history of malignancy.
Lifestyle factors such as fat consumption, alcohol consumption, education, and
socioeconomic status have also been associated with an increased incidence of breast
15 cancer although a direct cause and effect relationship has not been established. While
these risk factors are statistically significant, their weak association with breast cancer
limited their usefulness. Most women who develop breast cancer have none of the risk
factors listed above, other than the risk that comes with growing older. NIH Publication
No. 00-1556 (2000).

20 Current screening methods for detecting cancer, such as breast self exam,
ultrasound, and mammography have drawbacks that reduce their effectiveness or prevent
their widespread adoption. Breast self exams, while useful, are unreliable for the
detection of breast cancer in the initial stages where the tumor is small and difficult to
detect by palpitation. Ultrasound measurements require skilled operators at an increased
25 expense. Mammography, while sensitive, is subject to over diagnosis in the detection of
lesions that have questionable malignant potential. There is also the fear of the radiation
used in mammography because prior chest radiation is a factor associated with an
increase incidence of breast cancer.

At this time, there are no adequate methods of breast cancer prevention. The
30 current methods of breast cancer prevention involve prophylactic mastectomy
(mastectomy performed before cancer diagnosis) and chemoprevention (chemotherapy

before cancer diagnosis) which are drastic measures that limit their adoption even among women with increased risk of breast cancer. Bevers, *supra*.

A number of genetic markers have been associated with breast cancer. Examples of these markers include carcinoembryonic antigen (CEA) (Mughal et al., 249 JAMA 1881 (1983)) MUC-1 (Frische and Liu, 22 J. Clin. Ligand 320 (2000)), HER-2/neu (Haris et al., 15 Proc.Am.Soc.Clin.Oncology. A96 (1996)), uPA, PAI-1, LPA, LPC, RAK and BRCA (Esteva and Fritsche, *Serum and Tissue Markers for Breast Cancer*, in BREAST CANCER, 286-308 (2001)). These markers have problems with limited sensitivity, low correlation, and false negatives which limit their use for initial diagnosis. For example, while the BRCA1 gene mutation is useful as an indicator of an increased risk for breast cancer, it has limited use in cancer diagnosis because only 6.2 % of breast cancers are BRCA1 positive. Malone et al., 279 JAMA 922 (1998). *See also*, Mewman et al., 279 JAMA 915 (1998) (correlation of only 3.3%).

Breast cancers are diagnosed into the appropriate stage categories recognizing that different treatments are more effective for different stages of cancer. Stage TX indicates that primary tumor cannot be assessed (i.e., tumor was removed or breast tissue was removed). Stage T0 is characterized by abnormalities such as hyperplasia but with no evidence of primary tumor. Stage Tis is characterized by carcinoma in situ, intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor. Stage T1 is characterized as having a tumor of 2 cm or less in the greatest dimension. Within stage T1, Tmic indicates microinvasion of 0.1 cm or less, T1a indicates a tumor of between 0.1 to 0.5 cm, T1b indicates a tumor of between 0.5 to 1 cm, and T1c indicates tumors of between 1 cm to 2 cm. Stage T2 is characterized by tumors from 2 cm to 5 cm in the greatest dimension. Tumors greater than 5 cm in size are classified as stage T4. Within stage T4, T4a indicates extension of the tumor to the chest wall, T4b indicates edema or ulceration of the skin of the breast or satellite skin nodules confined to the same breast, T4c indicates a combination of T4a and T4b, and T4d indicates inflammatory carcinoma. AJCC Cancer Staging Handbook pp. 159-70 (Irvin D. Fleming et al. eds., 5th ed. 1998). In addition to standard staging, breast tumors may be classified according to their estrogen receptor and progesterone receptor protein status. Fisher et al., 7 Breast Cancer Research and Treatment 147 (1986). Additional pathological status, such as HER2/neu status may also be useful. Thor et al., 90

J.Nat'l.Cancer Inst. 1346 (1998); Paik et al., 90 J.Nat'l.Cancer Inst. 1361 (1998); Hutchins et al., 17 Proc.Am.Soc.Clin.Oncology A2 (1998).; and Simpson et al., 18 J.Clin.Oncology 2059 (2000).

In addition to the staging of the primary tumor, breast cancer metastases to regional lymph nodes may be staged. Stage NX indicates that the lymph nodes cannot be assessed (e.g., previously removed). Stage N0 indicates no regional lymph node metastasis. Stage N1 indicates metastasis to movable ipsilateral axillary lymph nodes. Stage N2 indicates metastasis to ipsilateral axillary lymph nodes fixed to one another or to other structures. Stage N3 indicates metastasis to ipsilateral internal mammary lymph nodes. Id.

Stage determination has potential prognostic value and provides criteria for designing optimal therapy. Simpson et al., 18 J. Clin. Oncology 2059 (2000). Generally, pathological staging of breast cancer is preferable to clinical staging because the former gives a more accurate prognosis. However, clinical staging would be preferred if it were as accurate as pathological staging because it does not depend on an invasive procedure to obtain tissue for pathological evaluation. Staging of breast cancer would be improved by detecting new markers in cells, tissues, or bodily fluids which could differentiate between different stages of invasion. Progress in this field will allow more rapid and reliable method for treating breast cancer patients.

Treatment of breast cancer is generally decided after an accurate staging of the primary tumor. Primary treatment options include breast conserving therapy (lumpectomy, breast irradiation, and surgical staging of the axilla), and modified radical mastectomy. Additional treatments include chemotherapy, regional irradiation, and, in extreme cases, terminating estrogen production by ovarian ablation.

Until recently, the customary treatment for all breast cancer was mastectomy. Fonseca et al., 127 Annals of Internal Medicine 1013 (1997). However, recent data indicate that less radical procedures may be equally effective, in terms of survival, for early stage breast cancer. Fisher et al., 16 J. of Clinical Oncology 441 (1998). The treatment options for a patient with early stage breast cancer (i.e., stage Tis) may be breast-sparing surgery followed by localized radiation therapy at the breast. Alternatively, mastectomy optionally coupled with radiation or breast reconstruction may

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be employed. These treatment methods are equally effective in the early stages of breast cancer.

Patients with stage I and stage II breast cancer require surgery with chemotherapy and/or hormonal therapy. Surgery is of limited use in Stage III and stage IV patients.

- 5 Thus, these patients are better candidates for chemotherapy and radiation therapy with surgery limited to biopsy to permit initial staging or subsequent restaging because cancer is rarely curative at this stage of the disease. AJCC Cancer Staging Handbook 84, ¶. 164-65 (Irvin D. Fleming et al. eds., 5th ed. 1998).

- 10 In an effort to provide more treatment options to patients, efforts are underway to define an earlier stage of breast cancer with low recurrence which could be treated with lumpectomy without postoperative radiation treatment. While a number of attempts have been made to classify early stage breast cancer, no consensus recommendation on postoperative radiation treatment has been obtained from these studies. Page et al., 75 Cancer 1219 (1995); Fisher et al., 75 Cancer 1223 (1995); Silverstein et al., 77 Cancer 15 2267 (1996).

- As discussed above, each of the methods for diagnosing and staging breast cancer is limited by the technology employed. Accordingly, there is need for sensitive molecular and cellular markers for the detection of breast cancer. There is a need for molecular markers for the accurate staging, including clinical and pathological staging, of 20 breast cancers to optimize treatment methods. Finally, there is a need for sensitive molecular and cellular markers to monitor the progress of cancer treatments, including markers that can detect recurrence of breast cancers following remission.

- Other objects, features, advantages and aspects of the present invention will become apparent to those of skill in the art from the following description. It should be 25 understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

SUMMARY OF THE INVENTION

The present invention solves these and other needs in the art by providing nucleic acid molecules and polypeptides as well as antibodies, agonists and antagonists, thereto that may be used to identify, diagnose, monitor, stage, image and treat breast cancer and non-cancerous disease states in breast; identify and monitor breast tissue; and identify and design agonists and antagonists of polypeptides of the invention. The invention also provides gene therapy, methods for producing transgenic animals and cells, and methods for producing engineered breast tissue for treatment and research.

Accordingly, one object of the invention is to provide nucleic acid molecules that are specific to breast cells and/or breast tissue. These breast specific nucleic acids (BSNAs) may be a naturally-occurring cDNA, genomic DNA, RNA, or a fragment of one of these nucleic acids, or may be a non-naturally-occurring nucleic acid molecule. If the BSNA is genomic DNA, then the BSNA is a breast specific gene (BSG). In a preferred embodiment, the nucleic acid molecule encodes a polypeptide that is specific to breast. In a more preferred embodiment, the nucleic acid molecule encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 165 through 280. In another highly preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1 through 164. By nucleic acid molecule, it is also meant to be inclusive of sequences that selectively hybridize or exhibit substantial sequence similarity to a nucleic acid molecule encoding a BSP, or that selectively hybridize or exhibit substantial sequence similarity to a BSNA, as well as allelic variants of a nucleic acid molecule encoding a BSP, and allelic variants of a BSNA. Nucleic acid molecules comprising a part of a nucleic acid sequence that encodes a BSP or that comprises a part of a nucleic acid sequence of a BSNA are also provided.

A related object of the present invention is to provide a nucleic acid molecule comprising one or more expression control sequences controlling the transcription and/or translation of all or a part of a BSNA. In a preferred embodiment, the nucleic acid molecule comprises one or more expression control sequences controlling the transcription and/or translation of a nucleic acid molecule that encodes all or a fragment of a BSP.

Another object of the invention is to provide vectors and/or host cells comprising a nucleic acid molecule of the instant invention. In a preferred embodiment, the nucleic

acid molecule encodes all or a fragment of a BSP. In another preferred embodiment, the nucleic acid molecule comprises all or a part of a BSNA.

Another object of the invention is to provide methods for using the vectors and host cells comprising a nucleic acid molecule of the instant invention to recombinantly produce polypeptides of the invention.

Another object of the invention is to provide a polypeptide encoded by a nucleic acid molecule of the invention. In a preferred embodiment, the polypeptide is a BSP. The polypeptide may comprise either a fragment or a full-length protein as well as a mutant protein (mutein), fusion protein, homologous protein or a polypeptide encoded by an allelic variant of a BSP.

Another object of the invention is to provide an antibody that specifically binds to a polypeptide of the instant invention..

Another object of the invention is to provide agonists and antagonists of the nucleic acid molecules and polypeptides of the instant invention.

Another object of the invention is to provide methods for using the nucleic acid molecules to detect or amplify nucleic acid molecules that have similar or identical nucleic acid sequences compared to the nucleic acid molecules described herein. In a preferred embodiment, the invention provides methods of using the nucleic acid molecules of the invention for identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and non-cancerous disease states in breast. In another preferred embodiment, the invention provides methods of using the nucleic acid molecules of the invention for identifying and/or monitoring breast tissue. The nucleic acid molecules of the instant invention may also be used in gene therapy, for producing transgenic animals and cells, and for producing engineered breast tissue for treatment and research.

The polypeptides and/or antibodies of the instant invention may also be used to identify, diagnose, monitor, stage, image and treat breast cancer and non-cancerous disease states in breast. The invention provides methods of using the polypeptides of the invention to identify and/or monitor breast tissue, and to produce engineered breast tissue.

The agonists and antagonists of the instant invention may be used to treat breast cancer and non-cancerous disease states in breast and to produce engineered breast tissue.

Yet another object of the invention is to provide a computer readable means of storing the nucleic acid and amino acid sequences of the invention. The records of the computer readable means can be accessed for reading and displaying of sequences for comparison, alignment and ordering of the sequences of the invention to other sequences.

5 DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Techniques

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular
10 terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used in the art. The methods and techniques of the present invention are generally performed
15 according to conventional methods well-known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. *See, e.g.*, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press (1989) and Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 3d ed., Cold Spring Harbor
20 Press (2001); Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates (1992, and Supplements to 2000); Ausubel *et al.*, Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology – 4th Ed., Wiley & Sons (1999); Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1990); and Harlow and Lane, Using
25 Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1999); each of which is incorporated herein by reference in its entirety.

Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and
30 techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in

the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

- 5 A “nucleic acid molecule” of this invention refers to a polymeric form of nucleotides and includes both sense and antisense strands of RNA, cDNA, genomic DNA, and synthetic forms and mixed polymers of the above. A nucleotide refers to a ribonucleotide, deoxynucleotide or a modified form of either type of nucleotide. A “nucleic acid molecule” as used herein is synonymous with “nucleic acid” and
- 10 “polynucleotide.” The term “nucleic acid molecule” usually refers to a molecule of at least 10 bases in length, unless otherwise specified. The term includes single- and double-stranded forms of DNA. In addition, a polynucleotide may include either or both naturally-occurring and modified nucleotides linked together by naturally-occurring and/or non-naturally occurring nucleotide linkages.
- 15 The nucleic acid molecules may be modified chemically or biochemically or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those of skill in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates,
- 20 phosphotriesters, phosphoramidates, carbamates, etc.), charged linkages (*e.g.*, phosphorothioates, phosphorodithioates, etc.), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine, psoralen, etc.), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids, etc.) The term “nucleic acid molecule” also includes any topological conformation, including single-stranded, double-stranded, partially
- 25 duplexed, triplexed, hairpinned, circular and padlocked conformations. Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.
- 30 A “gene” is defined as a nucleic acid molecule that comprises a nucleic acid sequence that encodes a polypeptide and the expression control sequences that surround the nucleic acid sequence that encodes the polypeptide. For instance, a gene may

comprise a promoter, one or more enhancers, a nucleic acid sequence that encodes a polypeptide, downstream regulatory sequences and, possibly, other nucleic acid sequences involved in regulation of the expression of an RNA. As is well-known in the art, eukaryotic genes usually contain both exons and introns. The term “exon” refers to a nucleic acid sequence found in genomic DNA that is bioinformatically predicted and/or experimentally confirmed to contribute a contiguous sequence to a mature mRNA transcript. The term “intron” refers to a nucleic acid sequence found in genomic DNA that is predicted and/or confirmed to not contribute to a mature mRNA transcript, but rather to be “spliced out” during processing of the transcript.

10 A nucleic acid molecule or polypeptide is “derived” from a particular species if the nucleic acid molecule or polypeptide has been isolated from the particular species, or if the nucleic acid molecule or polypeptide is homologous to a nucleic acid molecule or polypeptide isolated from a particular species.

An “isolated” or “substantially pure” nucleic acid or polynucleotide (*e.g.*, an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components that naturally accompany the native polynucleotide in its natural host cell, *e.g.*, ribosomes, polymerases, or genomic sequences with which it is naturally associated. The term embraces a nucleic acid or polynucleotide that (1) has been removed from its naturally occurring environment, (2) is not associated with all or a portion of a polynucleotide in which the “isolated polynucleotide” is found in nature, (3) is operatively linked to a polynucleotide which it is not linked to in nature, (4) does not occur in nature as part of a larger sequence or (5) includes nucleotides or internucleoside bonds that are not found in nature. The term “isolated” or “substantially pure” also can be used in reference to recombinant or cloned DNA isolates, chemically synthesized polynucleotide analogs, or polynucleotide analogs that are biologically synthesized by heterologous systems. The term “isolated nucleic acid molecule” includes nucleic acid molecules that are integrated into a host cell chromosome at a heterologous site, recombinant fusions of a native fragment to a heterologous sequence, recombinant vectors present as episomes or as integrated into a host cell chromosome.

30 A “part” of a nucleic acid molecule refers to a nucleic acid molecule that comprises a partial contiguous sequence of at least 10 bases of the reference nucleic acid molecule. Preferably, a part comprises at least 15 to 20 bases of a reference nucleic acid

molecule. In theory, a nucleic acid sequence of 17 nucleotides is of sufficient length to occur at random less frequently than once in the three gigabase human genome, and thus to provide a nucleic acid probe that can uniquely identify the reference sequence in a nucleic acid mixture of genomic complexity. A preferred part is one that comprises a nucleic acid sequence that can encode at least 6 contiguous amino acid sequences (fragments of at least 18 nucleotides) because they are useful in directing the expression or synthesis of peptides that are useful in mapping the epitopes of the polypeptide encoded by the reference nucleic acid. *See, e.g., Geysen et al., Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1984); and United States Patent Nos. 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. A part may also comprise at least 25, 30, 35 or 40 nucleotides of a reference nucleic acid molecule, or at least 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides of a reference nucleic acid molecule. A part of a nucleic acid molecule may comprise no other nucleic acid sequences. Alternatively, a part of a nucleic acid may comprise other nucleic acid sequences from other nucleic acid molecules.

The term "oligonucleotide" refers to a nucleic acid molecule generally comprising a length of 200 bases or fewer. The term often refers to single-stranded deoxyribonucleotides, but it can refer as well to single- or double-stranded ribonucleotides, RNA:DNA hybrids and double-stranded DNAs, among others. Preferably, oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17, 18, 19 or 20 bases in length. Other preferred oligonucleotides are 25, 30, 35, 40, 45, 50, 55 or 60 bases in length. Oligonucleotides may be single-stranded, *e.g.* for use as probes or primers, or may be double-stranded, *e.g.* for use in the construction of a mutant gene. Oligonucleotides of the invention can be either sense or antisense oligonucleotides. An oligonucleotide can be derivatized or modified as discussed above for nucleic acid molecules.

Oligonucleotides, such as single-stranded DNA probe oligonucleotides, often are synthesized by chemical methods, such as those implemented on automated oligonucleotide synthesizers. However, oligonucleotides can be made by a variety of other methods, including *in vitro* recombinant DNA-mediated techniques and by expression of DNAs in cells and organisms. Initially, chemically synthesized DNAs typically are obtained without a 5' phosphate. The 5' ends of such oligonucleotides are

not substrates for phosphodiester bond formation by ligation reactions that employ DNA ligases typically used to form recombinant DNA molecules. Where ligation of such oligonucleotides is desired, a phosphate can be added by standard techniques, such as those that employ a kinase and ATP. The 3' end of a chemically synthesized
5 oligonucleotide generally has a free hydroxyl group and, in the presence of a ligase, such as T4 DNA ligase, readily will form a phosphodiester bond with a 5' phosphate of another polynucleotide, such as another oligonucleotide. As is well-known, this reaction can be prevented selectively, where desired, by removing the 5' phosphates of the other polynucleotide(s) prior to ligation.

- 10 The term "naturally-occurring nucleotide" referred to herein includes naturally-occurring deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "nucleotide linkages" referred to herein includes nucleotides linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate,
15 phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate, phosphoroamidate, and the like. *See e.g.*, LaPlanche *et al. Nucl. Acids Res.* 14:9081-9093 (1986); Stein *et al. Nucl. Acids Res.* 16:3209-3221 (1988); Zon *et al. Anti-Cancer Drug Design* 6:539-568 (1991); Zon *et al.*, in Eckstein (ed.) Oligonucleotides and Analogues: A Practical Approach, pp. 87-108, Oxford University Press (1991); United States Patent No.
20 5,151,510; Uhlmann and Peyman *Chemical Reviews* 90:543 (1990), the disclosures of which are hereby incorporated by reference.

- Unless specified otherwise, the left hand end of a polynucleotide sequence in sense orientation is the 5' end and the right hand end of the sequence is the 3' end. In addition, the left hand direction of a polynucleotide sequence in sense orientation is
25 referred to as the 5' direction, while the right hand direction of the polynucleotide sequence is referred to as the 3' direction. Further, unless otherwise indicated, each nucleotide sequence is set forth herein as a sequence of deoxyribonucleotides. It is intended, however, that the given sequence be interpreted as would be appropriate to the polynucleotide composition: for example, if the isolated nucleic acid is composed of
30 RNA, the given sequence intends ribonucleotides, with uridine substituted for thymidine.

The term "allelic variant" refers to one of two or more alternative naturally-occurring forms of a gene, wherein each gene possesses a unique nucleotide sequence.

In a preferred embodiment, different alleles of a given gene have similar or identical biological properties.

The term "percent sequence identity" in the context of nucleic acid sequences refers to the residues in two sequences which are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides. There are a number of different algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using FASTA, Gap or Bestfit, which are programs in Wisconsin Package Version 10.0, Genetics Computer Group (GCG), Madison, Wisconsin. FASTA, which includes, *e.g.*, the programs FASTA2 and FASTA3, provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, *Methods Enzymol.* 183: 63-98 (1990); Pearson, *Methods Mol. Biol.* 132: 185-219 (2000); Pearson, *Methods Enzymol.* 266: 227-258 (1996); Pearson, *J. Mol. Biol.* 276: 71-84 (1998); herein incorporated by reference). Unless otherwise specified, default parameters for a particular program or algorithm are used. For instance, percent sequence identity between nucleic acid sequences can be determined using FASTA with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) or using Gap with its default parameters as provided in GCG Version 6.1, herein incorporated by reference.

A reference to a nucleic acid sequence encompasses its complement unless otherwise specified. Thus, a reference to a nucleic acid molecule having a particular sequence should be understood to encompass its complementary strand, with its complementary sequence. The complementary strand is also useful, *e.g.*, for antisense therapy, hybridization probes and PCR primers.

In the molecular biology art, researchers use the terms "percent sequence identity", "percent sequence similarity" and "percent sequence homology" interchangeably. In this application, these terms shall have the same meaning with respect to nucleic acid sequences only.

The term "substantial similarity" or "substantial sequence similarity," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 50%, more preferably 60% of the nucleotide bases, usually at least about 70%, more usually at least about 80%, preferably at least about 90%, and more preferably at least about 95-98% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed above.

Alternatively, substantial similarity exists when a nucleic acid or fragment thereof hybridizes to another nucleic acid, to a strand of another nucleic acid, or to the complementary strand thereof, under selective hybridization conditions. Typically, selective hybridization will occur when there is at least about 55% sequence identity, preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90% sequence identity, over a stretch of at least about 14 nucleotides, more preferably at least 17 nucleotides, even more preferably at least 20, 25, 30, 35, 40, 50, 60, 70, 80, 90 or 100 nucleotides.

Nucleic acid hybridization will be affected by such conditions as salt concentration, temperature, solvents, the base composition of the hybridizing species, length of the complementary regions, and the number of nucleotide base mismatches between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. "Stringent hybridization conditions" and "stringent wash conditions" in the context of nucleic acid hybridization experiments depend upon a number of different physical parameters. The most important parameters include temperature of hybridization, base composition of the nucleic acids, salt concentration and length of the nucleic acid. One having ordinary skill in the art knows how to vary these parameters to achieve a particular stringency of hybridization. In general, "stringent hybridization" is performed at about 25°C below the thermal melting point (T_m) for the specific DNA hybrid under a particular set of conditions. "Stringent washing" is performed at temperatures about 5°C lower than the T_m for the specific DNA hybrid under a particular set of conditions. The T_m is the temperature at which 50% of the target sequence hybridizes to a perfectly matched probe. See Sambrook (1989), *supra*, p. 9.51, hereby incorporated by reference.

The T_m for a particular DNA-DNA hybrid can be estimated by the formula:

$$T_m = 81.5^\circ\text{C} + 16.6 (\log_{10}[\text{Na}^+]) + 0.41 (\text{fraction G} + \text{C}) - 0.63 (\% \text{ formamide}) - (600/l)$$

where l is the length of the hybrid in base pairs.

The T_m for a particular RNA-RNA hybrid can be estimated by the formula:

5 $T_m = 79.8^\circ\text{C} + 18.5 (\log_{10}[\text{Na}^+]) + 0.58 (\text{fraction G} + \text{C}) + 11.8 (\text{fraction G} + \text{C})^2 - 0.35$
(% formamide) - (820/ l).

The T_m for a particular RNA-DNA hybrid can be estimated by the formula:

$$T_m = 79.8^\circ\text{C} + 18.5 (\log_{10}[\text{Na}^+]) + 0.58 (\text{fraction G} + \text{C}) + 11.8 (\text{fraction G} + \text{C})^2 - 0.50$$

(% formamide) - (820/ l).

10 In general, the T_m decreases by 1-1.5°C for each 1% of mismatch between two nucleic acid sequences. Thus, one having ordinary skill in the art can alter hybridization and/or washing conditions to obtain sequences that have higher or lower degrees of sequence identity to the target nucleic acid. For instance, to obtain hybridizing nucleic acids that contain up to 10% mismatch from the target nucleic acid sequence, 10-15°C
15 would be subtracted from the calculated T_m of a perfectly matched hybrid, and then the hybridization and washing temperatures adjusted accordingly. Probe sequences may also hybridize specifically to duplex DNA under certain conditions to form triplex or other higher order DNA complexes. The preparation of such probes and suitable hybridization conditions are well-known in the art.

20 An example of stringent hybridization conditions for hybridization of complementary nucleic acid sequences having more than 100 complementary residues on a filter in a Southern or Northern blot or for screening a library is 50% formamide/6X SSC at 42°C for at least ten hours and preferably overnight (approximately 16 hours). Another example of stringent hybridization conditions is 6X SSC at 68°C without
25 formamide for at least ten hours and preferably overnight. An example of moderate stringency hybridization conditions is 6X SSC at 55°C without formamide for at least ten hours and preferably overnight. An example of low stringency hybridization conditions for hybridization of complementary nucleic acid sequences having more than 100 complementary residues on a filter in a Southern or Northern blot or for screening a
30 library is 6X SSC at 42°C for at least ten hours. Hybridization conditions to identify nucleic acid sequences that are similar but not identical can be identified by experimentally changing the hybridization temperature from 68°C to 42°C while keeping

the salt concentration constant (6X SSC), or keeping the hybridization temperature and salt concentration constant (*e.g.* 42°C and 6X SSC) and varying the formamide concentration from 50% to 0%. Hybridization buffers may also include blocking agents to lower background. These agents are well-known in the art. *See Sambrook et al.*

- 5 (1989), *supra*, pages 8.46 and 9.46-9.58, herein incorporated by reference. *See also* Ausubel (1992), *supra*, Ausubel (1999), *supra*, and Sambrook (2001), *supra*.

Wash conditions also can be altered to change stringency conditions. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (*see* Sambrook (1989), *supra*, for SSC buffer). Often the high stringency wash is preceded by a low stringency wash to remove excess probe. An exemplary medium stringency wash for duplex DNA of more than 100 base pairs is 1x SSC at 45°C for 15 minutes. An exemplary low stringency wash for such a duplex is 4x SSC at 40°C for 15 minutes. In general, signal-to-noise ratio of 2x or higher than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization.

- 15 As defined herein, nucleic acid molecules that do not hybridize to each other under stringent conditions are still substantially similar to one another if they encode polypeptides that are substantially identical to each other. This occurs, for example, when a nucleic acid molecule is created synthetically or recombinantly using high codon degeneracy as permitted by the redundancy of the genetic code.

20 Hybridization conditions for nucleic acid molecules that are shorter than 100 nucleotides in length (*e.g.*, for oligonucleotide probes) may be calculated by the formula: $T_m = 81.5^{\circ}\text{C} + 16.6(\log_{10}[\text{Na}^+]) + 0.41(\text{fraction G+C}) - (600/N)$, wherein N is change length and the $[\text{Na}^+]$ is 1 M or less. *See* Sambrook (1989), *supra*, p. 11.46. For hybridization of probes shorter than 100 nucleotides, hybridization is usually performed under stringent conditions (5-10°C below the T_m) using high concentrations (0.1-1.0 pmol/ml) of probe. *Id.* at p. 11.45. Determination of hybridization using mismatched probes, pools of degenerate probes or “guessmers,” as well as hybridization solutions and methods for empirically determining hybridization conditions are well-known in the art. *See, e.g.*, Ausubel (1999), *supra*; Sambrook (1989), *supra*, pp. 11.45-30 11.57.

The term “digestion” or “digestion of DNA” refers to catalytic cleavage of the DNA with a restriction enzyme that acts only at certain sequences in the DNA. The

various restriction enzymes referred to herein are commercially available and their reaction conditions, cofactors and other requirements for use are known and routine to the skilled artisan. For analytical purposes, typically, 1 μ g of plasmid or DNA fragment is digested with about 2 units of enzyme in about 20 μ l of reaction buffer. For the purpose of isolating DNA fragments for plasmid construction, typically 5 to 50 μ g of DNA are digested with 20 to 250 units of enzyme in proportionately larger volumes. Appropriate buffers and substrate amounts for particular restriction enzymes are described in standard laboratory manuals, such as those referenced below, and they are specified by commercial suppliers. Incubation times of about 1 hour at 37°C are ordinarily used, but conditions may vary in accordance with standard procedures, the supplier's instructions and the particulars of the reaction. After digestion, reactions may be analyzed, and fragments may be purified by electrophoresis through an agarose or polyacrylamide gel, using well-known methods that are routine for those skilled in the art.

The term "ligation" refers to the process of forming phosphodiester bonds between two or more polynucleotides, which most often are double-stranded DNAs. Techniques for ligation are well-known to the art and protocols for ligation are described in standard laboratory manuals and references, such as, *e.g.*, Sambrook (1989), *supra*.

Genome-derived "single exon probes," are probes that comprise at least part of an exon ("reference exon") and can hybridize detectably under high stringency conditions to transcript-derived nucleic acids that include the reference exon but do not hybridize detectably under high stringency conditions to nucleic acids that lack the reference exon. Single exon probes typically further comprise, contiguous to a first end of the exon portion, a first intronic and/or intergenic sequence that is identically contiguous to the exon in the genome, and may contain a second intronic and/or intergenic sequence that is identically contiguous to the exon in the genome. The minimum length of genome-derived single exon probes is defined by the requirement that the exonic portion be of sufficient length to hybridize under high stringency conditions to transcript-derived nucleic acids, as discussed above. The maximum length of genome-derived single exon probes is defined by the requirement that the probes contain portions of no more than one exon. The single exon probes may contain priming sequences not found in contiguity

with the rest of the probe sequence in the genome, which priming sequences are useful for PCR and other amplification-based technologies.

The term "microarray" or "nucleic acid microarray" refers to a substrate-bound collection of plural nucleic acids, hybridization to each of the plurality of bound nucleic acids being separately detectable. The substrate can be solid or porous, planar or non-planar, unitary or distributed. Microarrays or nucleic acid microarrays include all the devices so called in Schena (ed.), DNA Microarrays: A Practical Approach (Practical Approach Series), Oxford University Press (1999); *Nature Genet.* 21(1)(suppl.):1 - 60 (1999); Schena (ed.), Microarray Biochip: Tools and Technology, Eaton Publishing Company/BioTechniques Books Division (2000). These microarrays include substrate-bound collections of plural nucleic acids in which the plurality of nucleic acids are disposed on a plurality of beads, rather than on a unitary planar substrate, as is described, *inter alia*, in Brenner *et al.*, *Proc. Natl. Acad. Sci. USA* 97(4):1665-1670 (2000).

The term "mutated" when applied to nucleic acid molecules means that nucleotides in the nucleic acid sequence of the nucleic acid molecule may be inserted, deleted or changed compared to a reference nucleic acid sequence. A single alteration may be made at a locus (a point mutation) or multiple nucleotides may be inserted, deleted or changed at a single locus. In addition, one or more alterations may be made at any number of loci within a nucleic acid sequence. In a preferred embodiment, the nucleic acid molecule comprises the wild type nucleic acid sequence encoding a BSP or is a BSNA. The nucleic acid molecule may be mutated by any method known in the art including those mutagenesis techniques described *infra*.

The term "error-prone PCR" refers to a process for performing PCR under conditions where the copying fidelity of the DNA polymerase is low, such that a high rate of point mutations is obtained along the entire length of the PCR product. *See, e.g.*, Leung *et al.*, *Technique* 1: 11-15 (1989) and Caldwell *et al.*, *PCR Methods Applic.* 2: 28-33 (1992).

The term "oligonucleotide-directed mutagenesis" refers to a process which enables the generation of site-specific mutations in any cloned DNA segment of interest. *See, e.g.*, Reidhaar-Olson *et al.*, *Science* 241: 53-57 (1988).

The term "assembly PCR" refers to a process which involves the assembly of a PCR product from a mixture of small DNA fragments. A large number of different PCR

reactions occur in parallel in the same vial, with the products of one reaction priming the products of another reaction.

The term "sexual PCR mutagenesis" or "DNA shuffling" refers to a method of error-prone PCR coupled with forced homologous recombination between DNA
5 molecules of different but highly related DNA sequence *in vitro*, caused by random fragmentation of the DNA molecule based on sequence similarity, followed by fixation of the crossover by primer extension in an error-prone PCR reaction. *See, e.g., Stemmer, Proc. Natl. Acad. Sci. U.S.A.* 91: 10747-10751 (1994). DNA shuffling can be carried out between several related genes ("Family shuffling").

10 The term "*in vivo* mutagenesis" refers to a process of generating random mutations in any cloned DNA of interest which involves the propagation of the DNA in a strain of bacteria such as *E. coli* that carries mutations in one or more of the DNA repair pathways. These "mutator" strains have a higher random mutation rate than that of a wild-type parent. Propagating the DNA in a mutator strain will eventually generate
15 random mutations within the DNA.

The term "cassette mutagenesis" refers to any process for replacing a small region of a double-stranded DNA molecule with a synthetic oligonucleotide "cassette" that differs from the native sequence. The oligonucleotide often contains completely and/or partially randomized native sequence.

20 The term "recursive ensemble mutagenesis" refers to an algorithm for protein engineering (protein mutagenesis) developed to produce diverse populations of phenotypically related mutants whose members differ in amino acid sequence. This method uses a feedback mechanism to control successive rounds of combinatorial cassette mutagenesis. *See, e.g., Arkin et al., Proc. Natl. Acad. Sci. U.S.A.* 89: 7811-7815
25 (1992).

The term "exponential ensemble mutagenesis" refers to a process for generating combinatorial libraries with a high percentage of unique and functional mutants, wherein small groups of residues are randomized in parallel to identify, at each altered position, amino acids which lead to functional proteins. *See, e.g., Delegrave et al., Biotechnology Research* 11: 1548-1552 (1993); Arnold, *Current Opinion in Biotechnology* 4: 450-455
30 (1993). Each of the references mentioned above are hereby incorporated by reference in its entirety.

“Operatively linked” expression control sequences refers to a linkage in which the expression control sequence is contiguous with the gene of interest to control the gene of interest, as well as expression control sequences that act in *trans* or at a distance to control the gene of interest.

5 The term “expression control sequence” as used herein refers to polynucleotide sequences which are necessary to affect the expression of coding sequences to which they are operatively linked. Expression control sequences are sequences which control the transcription, post-transcriptional events and translation of nucleic acid sequences. Expression control sequences include appropriate transcription initiation, termination,
10 promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (*e.g.*, ribosome binding sites); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such
15 control sequences generally include the promoter, ribosomal binding site, and transcription termination sequence. The term “control sequences” is intended to include, at a minimum, all components whose presence is essential for expression, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences.

20 The term “vector,” as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a “plasmid”, which refers to a circular double-stranded DNA loop into which additional DNA segments may be ligated. Other vectors include cosmids, bacterial artificial chromosomes (BAC) and yeast artificial chromosomes (YAC). Another type of
25 vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Viral vectors that infect bacterial cells are referred to as bacteriophages. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication). Other vectors can be integrated into the genome of a host cell upon introduction into the host cell, and
30 thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as “recombinant expression vectors” (or simply, “expression

vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include other forms of expression vectors that
5 serve equivalent functions.

The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which an expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding
10 generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

As used herein, the phrase "open reading frame" and the equivalent acronym "ORF" refer to that portion of a transcript-derived nucleic acid that can be translated in
15 its entirety into a sequence of contiguous amino acids. As so defined, an ORF has length, measured in nucleotides, exactly divisible by 3. As so defined, an ORF need not encode the entirety of a natural protein.

As used herein, the phrase "ORF-encoded peptide" refers to the predicted or actual translation of an ORF.

20 As used herein, the phrase "degenerate variant" of a reference nucleic acid sequence intends all nucleic acid sequences that can be directly translated, using the standard genetic code, to provide an amino acid sequence identical to that translated from the reference nucleic acid sequence.

The term "polypeptide" encompasses both naturally-occurring and non-naturally-
25 occurring proteins and polypeptides, polypeptide fragments and polypeptide mutants, derivatives and analogs. A polypeptide may be monomeric or polymeric. Further, a polypeptide may comprise a number of different modules within a single polypeptide each of which has one or more distinct activities. A preferred polypeptide in accordance with the invention comprises a BSP encoded by a nucleic acid molecule of the instant
30 invention, as well as a fragment, mutant, analog and derivative thereof.

The term "isolated protein" or "isolated polypeptide" is a protein or polypeptide that by virtue of its origin or source of derivation (1) is not associated with naturally

associated components that accompany it in its native state, (2) is free of other proteins from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be

5 “isolated” from its naturally associated components. A polypeptide or protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well-known in the art.

A protein or polypeptide is “substantially pure,” “substantially homogeneous” or “substantially purified” when at least about 60% to 75% of a sample exhibits a single

10 species of polypeptide. The polypeptide or protein may be monomeric or multimeric. A substantially pure polypeptide or protein will typically comprise about 50%, 60%, 70%, 80% or 90% W/W of a protein sample, more usually about 95%, and preferably will be over 99% pure. Protein purity or homogeneity may be indicated by a number of means well-known in the art, such as polyacrylamide gel electrophoresis of a protein sample,

15 followed by visualizing a single polypeptide band upon staining the gel with a stain well-known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well-known in the art for purification.

The term “polypeptide fragment” as used herein refers to a polypeptide of the instant invention that has an amino-terminal and/or carboxy-terminal deletion compared

20 to a full-length polypeptide. In a preferred embodiment, the polypeptide fragment is a contiguous sequence in which the amino acid sequence of the fragment is identical to the corresponding positions in the naturally-occurring sequence. Fragments typically are at least 5, 6, 7, 8, 9 or 10 amino acids long, preferably at least 12, 14, 16 or 18 amino acids long, more preferably at least 20 amino acids long, more preferably at least 25, 30, 35, 40

25 or 45, amino acids, even more preferably at least 50 or 60 amino acids long, and even more preferably at least 70 amino acids long.

A “derivative” refers to polypeptides or fragments thereof that are substantially similar in primary structural sequence but which include, *e.g.*, *in vivo* or *in vitro* chemical and biochemical modifications that are not found in the native polypeptide. Such

30 modifications include, for example, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid

derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Other modification include, *e.g.*, labeling with radionuclides, and various enzymatic modifications, as will be readily appreciated by those skilled in the art. A variety of methods for labeling polypeptides and of substituents or labels useful for such purposes are well-known in the art, and include radioactive isotopes such as ^{125}I , ^{32}P , ^{35}S , and ^3H , ligands which bind to labeled antiligands (*e.g.*, antibodies), fluorophores, chemiluminescent agents, enzymes, and antiligands which can serve as specific binding pair members for a labeled ligand. The choice of label depends on the sensitivity required, ease of conjugation with the primer, stability requirements, and available instrumentation. Methods for labeling polypeptides are well-known in the art. *See* Ausubel (1992), *supra*; Ausubel (1999), *supra*, herein incorporated by reference.

The term "fusion protein" refers to polypeptides of the instant invention comprising polypeptides or fragments coupled to heterologous amino acid sequences. Fusion proteins are useful because they can be constructed to contain two or more desired functional elements from two or more different proteins. A fusion protein comprises at least 10 contiguous amino acids from a polypeptide of interest, more preferably at least 20 or 30 amino acids, even more preferably at least 40, 50 or 60 amino acids, yet more preferably at least 75, 100 or 125 amino acids. Fusion proteins can be produced recombinantly by constructing a nucleic acid sequence which encodes the polypeptide or a fragment thereof in frame with a nucleic acid sequence encoding a different protein or peptide and then expressing the fusion protein. Alternatively, a fusion protein can be produced chemically by crosslinking the polypeptide or a fragment thereof to another protein.

The term "analog" refers to both polypeptide analogs and non-peptide analogs. The term "polypeptide analog" as used herein refers to a polypeptide of the instant invention that is comprised of a segment of at least 25 amino acids that has substantial

identity to a portion of an amino acid sequence but which contains non-natural amino acids or non-natural inter-residue bonds. In a preferred embodiment, the analog has the same or similar biological activity as the native polypeptide. Typically, polypeptide analogs comprise a conservative amino acid substitution (or insertion or deletion) with respect to the naturally-occurring sequence. Analog typically are at least 20 amino acids long, preferably at least 50 amino acids long or longer, and can often be as long as a full-length naturally-occurring polypeptide.

The term "non-peptide analog" refers to a compound with properties that are analogous to those of a reference polypeptide of the instant invention. A non-peptide compound may also be termed a "peptide mimetic" or a "peptidomimetic." Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to useful peptides may be used to produce an equivalent effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.*, a polypeptide that has a desired biochemical property or pharmacological activity), but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: --CH₂NH--, --CH₂S--, --CH₂-CH₂--, --CH=CH--(cis and trans), --COCH₂--, --CH(OH)CH₂--, and --CH₂SO--, by methods well-known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo *et al.*, *Ann. Rev. Biochem.* 61:387-418 (1992), incorporated herein by reference). For example, one may add internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

A "polypeptide mutant" or "mutein" refers to a polypeptide of the instant invention whose sequence contains substitutions, insertions or deletions of one or more amino acids compared to the amino acid sequence of a native or wild-type protein. A mutein may have one or more amino acid point substitutions, in which a single amino acid at a position has been changed to another amino acid, one or more insertions and/or deletions, in which one or more amino acids are inserted or deleted, respectively, in the sequence of the naturally-occurring protein, and/or truncations of the amino acid

- sequence at either or both the amino or carboxy termini. Further, a mutein may have the same or different biological activity as the naturally-occurring protein. For instance, a mutein may have an increased or decreased biological activity. A mutein has at least 50% sequence similarity to the wild type protein, preferred is 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are muteins having 80%, 85% or 90% sequence similarity to the wild type protein. In an even more preferred embodiment, a mutein exhibits 95% sequence identity, even more preferably 97%, even more preferably 98% and even more preferably 99%. Sequence similarity may be measured by any common sequence analysis algorithm, such as Gap or Bestfit.
- Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinity or enzymatic activity, and (5) confer or modify other physicochemical or functional properties of such analogs. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally-occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. In a preferred embodiment, the amino acid substitutions are moderately conservative substitutions or conservative substitutions. In a more preferred embodiment, the amino acid substitutions are conservative substitutions. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (*e.g.*, a replacement amino acid should not tend to disrupt a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in Creighton (ed.), Proteins, Structures and Molecular Principles, W. H. Freeman and Company (1984); Branden *et al.* (ed.), Introduction to Protein Structure, Garland Publishing (1991); Thornton *et al.*, *Nature* 354:105-106 (1991), each of which are incorporated herein by reference.

As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See Golub *et al.* (eds.), Immunology - A Synthesis 2nd Ed., Sinauer Associates (1991), which is incorporated herein by reference. Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as -, -disubstituted amino acids, N-alkyl amino acids, and other unconventional amino

acids may also be suitable components for polypeptides of the present invention.

Examples of unconventional amino acids include: 4-hydroxyproline, γ -carboxyglutamate,

-N,N,N-trimethyllysine, -N-acetyllysine, O-phosphoserine, N-acetylserine,

N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, s-N-methylarginine, and other

5 similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the lefthand direction is the amino terminal direction and the right hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

A protein has "homology" or is "homologous" to a protein from another organism
10 if the encoded amino acid sequence of the protein has a similar sequence to the encoded amino acid sequence of a protein of a different organism and has a similar biological activity or function. Alternatively, a protein may have homology or be homologous to another protein if the two proteins have similar amino acid sequences and have similar biological activities or functions. Although two proteins are said to be "homologous,"
15 this does not imply that there is necessarily an evolutionary relationship between the proteins. Instead, the term "homologous" is defined to mean that the two proteins have similar amino acid sequences and similar biological activities or functions. In a preferred embodiment, a homologous protein is one that exhibits 50% sequence similarity to the wild type protein, preferred is 60% sequence similarity, more preferred is 70% sequence
20 similarity. Even more preferred are homologous proteins that exhibit 80%, 85% or 90% sequence similarity to the wild type protein. In a yet more preferred embodiment, a homologous protein exhibits 95%, 97%, 98% or 99% sequence similarity.

When "sequence similarity" is used in reference to proteins or peptides, it is recognized that residue positions that are not identical often differ by conservative amino
25 acid substitutions. In a preferred embodiment, a polypeptide that has "sequence similarity" comprises conservative or moderately conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (*e.g.*, charge or hydrophobicity). In general, a conservative amino
30 acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted

upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. *See, e.g., Pearson, Methods Mol. Biol.* 24: 307-31 (1994), herein incorporated by reference.

For instance, the following six groups each contain amino acids that are

5 conservative substitutions for one another:

- 1) Serine (S), Threonine (T);
- 2) Aspartic Acid (D), Glutamic Acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 10 5) Isoleucine (I), Leucine (L), Methionine (M), Alanine (A), Valine (V), and
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al., Science* 256: 1443-45 (1992), herein incorporated by reference. A “moderately conservative” replacement is
15 any change having a nonnegative value in the PAM250 log-likelihood matrix.

Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid
20 substitutions. For instance, GCG contains programs such as “Gap” and “Bestfit” which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. *See, e.g., GCG Version 6.1. Other programs include FASTA, discussed supra.*

25 A preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially blastp or tblastn. *See, e.g., Altschul et al., J. Mol. Biol.* 215: 403-410 (1990); Altschul *et al., Nucleic Acids Res.* 25:3389-402 (1997); herein incorporated by reference. Preferred parameters for blastp are:

- 30 Expectation value: 10 (default)
 Filter: seg (default)
 Cost to open a gap: 11 (default)

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Cost to extend a gap: 1 (default)
 Max. alignments: 100 (default)
 Word size: 11 (default)
 No. of descriptions: 100 (default)
 5 Penalty Matrix: BLOSUM62

The length of polypeptide sequences compared for homology will generally be at least about 16 amino acid residues, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. When searching a database containing sequences from a large number
 10 of different organisms, it is preferable to compare amino acid sequences.

Database searching using amino acid sequences can be measured by algorithms other than blastp are known in the art. For instance, polypeptide sequences can be compared using FASTA, a program in GCG Version 6.1. FASTA (*e.g.*, FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best
 15 overlap between the query and search sequences (Pearson (1990), *supra*; Pearson (2000), *supra*. For example, percent sequence identity between amino acid sequences can be determined using FASTA with its default or recommended parameters (a word size of 2 and the PAM250 scoring matrix), as provided in GCG Version 6.1, herein incorporated by reference.

20 An "antibody" refers to an intact immunoglobulin, or to an antigen-binding portion thereof that competes with the intact antibody for specific binding to a molecular species, *e.g.*, a polypeptide of the instant invention. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen-binding portions include, *inter alia*, Fab, Fab', F(ab')₂, Fv,
 25 dAb, and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. An Fab fragment is a monovalent fragment consisting of the VL, VH, CL and CH1 domains; an F(ab')₂ fragment is a bivalent fragment comprising two Fab
 30 fragments linked by a disulfide bridge at the hinge region; an Fd fragment consists of the VH and CH1 domains; an Fv fragment consists of the VL and VH domains of a single

arm of an antibody; and a dAb fragment consists of a VH domain. *See, e.g., Ward et al., Nature* 341: 544-546 (1989).

By "bind specifically" and "specific binding" is here intended the ability of the antibody to bind to a first molecular species in preference to binding to other molecular species with which the antibody and first molecular species are admixed. An antibody is said specifically to "recognize" a first molecular species when it can bind specifically to that first molecular species.

A single-chain antibody (scFv) is an antibody in which a VL and VH region are paired to form a monovalent molecule via a synthetic linker that enables them to be made as a single protein chain. *See, e.g., Bird et al., Science* 242: 423-426 (1988); Huston *et al., Proc. Natl. Acad. Sci. USA* 85: 5879-5883 (1988). Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites. *See e.g., Holliger et al., Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993); Poljak *et al., Structure* 2: 1121-1123 (1994). One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an immunoadhesin. An immunoadhesin may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the immunoadhesin to specifically bind to a particular antigen of interest. A chimeric antibody is an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies.

An antibody may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For instance, a naturally-occurring immunoglobulin has two identical binding sites, a single-chain antibody or Fab fragment has one binding site, while a "bispecific" or "bifunctional" antibody has two different binding sites.

An "isolated antibody" is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. It is known that

purified proteins, including purified antibodies, may be stabilized with non-naturally-associated components. The non-naturally-associated component may be a protein, such as albumin (*e.g.*, BSA) or a chemical such as polyethylene glycol (PEG).

5 A “neutralizing antibody” or “an inhibitory antibody” is an antibody that inhibits the activity of a polypeptide or blocks the binding of a polypeptide to a ligand that normally binds to it. An “activating antibody” is an antibody that increases the activity of a polypeptide.

The term “epitope” includes any protein determinant capable of specifically binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist
10 of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is less than 1 μ M, preferably less than 100 nM and most preferably less than 10 nM.

15 The term “patient” as used herein includes human and veterinary subjects.

Throughout this specification and claims, the word “comprise,” or variations such as “comprises” or “comprising,” will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

20 The term “breast specific” refers to a nucleic acid molecule or polypeptide that is expressed predominantly in the breast as compared to other tissues in the body. In a preferred embodiment, a “breast specific” nucleic acid molecule or polypeptide is expressed at a level that is 5-fold higher than any other tissue in the body. In a more preferred embodiment, the “breast specific” nucleic acid molecule or polypeptide is
25 expressed at a level that is 10-fold higher than any other tissue in the body, more preferably at least 15-fold, 20-fold, 25-fold, 50-fold or 100-fold higher than any other tissue in the body. Nucleic acid molecule levels may be measured by nucleic acid hybridization, such as Northern blot hybridization, or quantitative PCR. Polypeptide levels may be measured by any method known to accurately quantitate protein levels,
30 such as Western blot analysis.

Nucleic Acid Molecules, Regulatory Sequences, Vectors, Host Cells and Recombinant Methods of Making Polypeptides

Nucleic Acid Molecules

5 One aspect of the invention provides isolated nucleic acid molecules that are specific to the breast or to breast cells or tissue or that are derived from such nucleic acid molecules. These isolated breast specific nucleic acids (BSNAs) may comprise a cDNA, a genomic DNA, RNA, or a fragment of one of these nucleic acids, or may be a non-naturally-occurring nucleic acid molecule. In a preferred embodiment, the nucleic acid
10 molecule encodes a polypeptide that is specific to breast, a breast-specific polypeptide (BSP). In a more preferred embodiment, the nucleic acid molecule encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 165 through 280. In another highly preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1 through 164.

15 A BSNA may be derived from a human or from another animal. In a preferred embodiment, the BSNA is derived from a human or other mammal. In a more preferred embodiment, the BSNA is derived from a human or other primate. In an even more preferred embodiment, the BSNA is derived from a human.

 By "nucleic acid molecule" for purposes of the present invention, it is also meant
20 to be inclusive of nucleic acid sequences that selectively hybridize to a nucleic acid molecule encoding a BSNA or a complement thereof. The hybridizing nucleic acid molecule may or may not encode a polypeptide or may not encode a BSP. However, in a preferred embodiment, the hybridizing nucleic acid molecule encodes a BSP. In a more preferred embodiment, the invention provides a nucleic acid molecule that selectively
25 hybridizes to a nucleic acid molecule that encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 165 through 280. In an even more preferred embodiment, the invention provides a nucleic acid molecule that selectively hybridizes to a nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO: 1 through 164.

 In a preferred embodiment, the nucleic acid molecule selectively hybridizes to a
30 nucleic acid molecule encoding a BSP under low stringency conditions. In a more preferred embodiment, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule encoding a BSP under moderate stringency conditions. In a more preferred embodiment, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule

encoding a BSP under high stringency conditions. In an even more preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high stringency conditions to a nucleic acid molecule encoding a polypeptide comprising an amino acid sequence of SEQ ID NO: 165 through 280. In a yet more preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high stringency conditions to a nucleic acid molecule comprising a nucleic acid sequence selected from SEQ ID NO: 1 through 164. In a preferred embodiment of the invention, the hybridizing nucleic acid molecule may be used to express recombinantly a polypeptide of the invention.

10 By "nucleic acid molecule" as used herein it is also meant to be inclusive of sequences that exhibits substantial sequence similarity to a nucleic acid encoding a BSP or a complement of the encoding nucleic acid molecule. In a preferred embodiment, the nucleic acid molecule exhibits substantial sequence similarity to a nucleic acid molecule encoding human BSP. In a more preferred embodiment, the nucleic acid molecule exhibits substantial sequence similarity to a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 165 through 280. In a preferred embodiment, the similar nucleic acid molecule is one that has at least 60% sequence identity with a nucleic acid molecule encoding a BSP, such as a polypeptide having an amino acid sequence of SEQ ID NO: 165 through 280, more preferably at least 70%, even more preferably at least 80% and even more preferably at least 85%. In a more preferred embodiment, the similar nucleic acid molecule is one that has at least 90% sequence identity with a nucleic acid molecule encoding a BSP, more preferably at least 95%, more preferably at least 97%, even more preferably at least 98%, and still more preferably at least 99%. In another highly preferred embodiment, the nucleic acid molecule is one that has at least 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity with a nucleic acid molecule encoding a BSP.

In another preferred embodiment, the nucleic acid molecule exhibits substantial sequence similarity to a BSNA or its complement. In a more preferred embodiment, the nucleic acid molecule exhibits substantial sequence similarity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1 through 164. In a preferred embodiment, the nucleic acid molecule is one that has at least 60% sequence identity with a BSNA, such as one having a nucleic acid sequence of SEQ ID NO: 1 through 164,

more preferably at least 70%, even more preferably at least 80% and even more preferably at least 85%. In a more preferred embodiment, the nucleic acid molecule is one that has at least 90% sequence identity with a BSNA, more preferably at least 95%, more preferably at least 97%, even more preferably at least 98%, and still more preferably at least 99%. In another highly preferred embodiment, the nucleic acid molecule is one that has at least 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity with a BSNA.

A nucleic acid molecule that exhibits substantial sequence similarity may be one that exhibits sequence identity over its entire length to a BSNA or to a nucleic acid molecule encoding a BSP, or may be one that is similar over only a part of its length. In this case, the part is at least 50 nucleotides of the BSNA or the nucleic acid molecule encoding a BSP, preferably at least 100 nucleotides, more preferably at least 150 or 200 nucleotides, even more preferably at least 250 or 300 nucleotides, still more preferably at least 400 or 500 nucleotides.

The substantially similar nucleic acid molecule may be a naturally-occurring one that is derived from another species, especially one derived from another primate, wherein the similar nucleic acid molecule encodes an amino acid sequence that exhibits significant sequence identity to that of SEQ ID NO: 165 through 280 or demonstrates significant sequence identity to the nucleotide sequence of SEQ ID NO: 1 through 164.

The similar nucleic acid molecule may also be a naturally-occurring nucleic acid molecule from a human, when the BSNA is a member of a gene family. The similar nucleic acid molecule may also be a naturally-occurring nucleic acid molecule derived from a non-primate, mammalian species, including without limitation, domesticated species, *e.g.*, dog, cat, mouse, rat, rabbit, hamster, cow, horse and pig; and wild animals, *e.g.*, monkey, fox, lions, tigers, bears, giraffes, zebras, etc. The substantially similar nucleic acid molecule may also be a naturally-occurring nucleic acid molecule derived from a non-mammalian species, such as birds or reptiles. The naturally-occurring substantially similar nucleic acid molecule may be isolated directly from humans or other species. In another embodiment, the substantially similar nucleic acid molecule may be one that is experimentally produced by random mutation of a nucleic acid molecule. In another embodiment, the substantially similar nucleic acid molecule may be one that is experimentally produced by directed mutation of a BSNA. Further, the substantially

similar nucleic acid molecule may or may not be a BSNA. However, in a preferred embodiment, the substantially similar nucleic acid molecule is a BSNA.

By "nucleic acid molecule" it is also meant to be inclusive of allelic variants of a BSNA or a nucleic acid encoding a BSP. For instance, single nucleotide polymorphisms (SNPs) occur frequently in eukaryotic genomes. In fact, more than 1.4 million SNPs have already identified in the human genome, International Human Genome Sequencing Consortium, *Nature* 409: 860-921 (2001). Thus, the sequence determined from one individual of a species may differ from other allelic forms present within the population. Additionally, small deletions and insertions, rather than single nucleotide polymorphisms, are not uncommon in the general population, and often do not alter the function of the protein. Further, amino acid substitutions occur frequently among natural allelic variants, and often do not substantially change protein function.

In a preferred embodiment, the nucleic acid molecule comprising an allelic variant is a variant of a gene, wherein the gene is transcribed into an mRNA that encodes a BSP. In a more preferred embodiment, the gene is transcribed into an mRNA that encodes a BSP comprising an amino acid sequence of SEQ ID NO: 165 through 280. In another preferred embodiment, the allelic variant is a variant of a gene, wherein the gene is transcribed into an mRNA that is a BSNA. In a more preferred embodiment, the gene is transcribed into an mRNA that comprises the nucleic acid sequence of SEQ ID NO: 1 through 164. In a preferred embodiment, the allelic variant is a naturally-occurring allelic variant in the species of interest. In a more preferred embodiment, the species of interest is human.

By "nucleic acid molecule" it is also meant to be inclusive of a part of a nucleic acid sequence of the instant invention. The part may or may not encode a polypeptide, and may or may not encode a polypeptide that is a BSP. However, in a preferred embodiment, the part encodes a BSP. In one aspect, the invention comprises a part of a BSNA. In a second aspect, the invention comprises a part of a nucleic acid molecule that hybridizes or exhibits substantial sequence similarity to a BSNA. In a third aspect, the invention comprises a part of a nucleic acid molecule that is an allelic variant of a BSNA. In a fourth aspect, the invention comprises a part of a nucleic acid molecule that encodes a BSP. A part comprises at least 10 nucleotides, more preferably at least 15, 17, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides.

The maximum size of a nucleic acid part is one nucleotide shorter than the sequence of the nucleic acid molecule encoding the full-length protein.

By "nucleic acid molecule" it is also meant to be inclusive of sequence that encoding a fusion protein, a homologous protein, a polypeptide fragment, a mutin or a
5 polypeptide analog, as described below.

Nucleotide sequences of the instantly-described nucleic acids were determined by sequencing a DNA molecule that had resulted, directly or indirectly, from at least one enzymatic polymerization reaction (*e.g.*, reverse transcription and/or polymerase chain reaction) using an automated sequencer (such as the MegaBACE™ 1000, Molecular
10 Dynamics, Sunnyvale, CA, USA). Further, all amino acid sequences of the polypeptides of the present invention were predicted by translation from the nucleic acid sequences so determined, unless otherwise specified.

In a preferred embodiment of the invention, the nucleic acid molecule contains modifications of the native nucleic acid molecule. These modifications include
15 nonnative internucleoside bonds, post-synthetic modifications or altered nucleotide analogues. One having ordinary skill in the art would recognize that the type of modification that can be made will depend upon the intended use of the nucleic acid molecule. For instance, when the nucleic acid molecule is used as a hybridization probe, the range of such modifications will be limited to those that permit sequence-
20 discriminating base pairing of the resulting nucleic acid. When used to direct expression of RNA or protein *in vitro* or *in vivo*, the range of such modifications will be limited to those that permit the nucleic acid to function properly as a polymerization substrate. When the isolated nucleic acid is used as a therapeutic agent, the modifications will be limited to those that do not confer toxicity upon the isolated nucleic acid.

25 In a preferred embodiment, isolated nucleic acid molecules can include nucleotide analogues that incorporate labels that are directly detectable, such as radiolabels or fluorophores, or nucleotide analogues that incorporate labels that can be visualized in a subsequent reaction, such as biotin or various haptens. In a more preferred embodiment, the labeled nucleic acid molecule may be used as a hybridization probe.

30 Common radiolabeled analogues include those labeled with ³³P, ³²P, and ³⁵S, such as ³²P-dATP, ³²P-dCTP, ³²P-dGTP, ³²P-dTTP, ³²P-3'dATP, ³²P-ATP, ³²P-CTP, ³²P-GTP, ³²P-UTP, ³⁵S-dATP, ³⁵S-GTP, ³³P-dATP, and the like.

Commercially available fluorescent nucleotide analogues readily incorporated into the nucleic acids of the present invention include Cy3-dCTP, Cy3-dUTP, Cy5-dCTP, Cy3-dUTP (Amersham Pharmacia Biotech, Piscataway, New Jersey, USA), fluorescein-12-dUTP, tetramethylrhodamine-6-dUTP, Texas Red®-5-dUTP, Cascade Blue®-7-dUTP, BODIPY® FL-14-dUTP, BODIPY® TMR-14-dUTP, BODIPY® TR-14-dUTP, Rhodamine Green™-5-dUTP, Oregon Green® 488-5-dUTP, Texas Red®-12-dUTP, BODIPY® 630/650-14-dUTP, BODIPY® 650/665-14-dUTP, Alexa Fluor® 488-5-dUTP, Alexa Fluor® 532-5-dUTP, Alexa Fluor® 568-5-dUTP, Alexa Fluor® 594-5-dUTP, Alexa Fluor® 546-14-dUTP, fluorescein-12-UTP, tetramethylrhodamine-6-UTP, Texas Red®-5-UTP, Cascade Blue®-7-UTP, BODIPY® FL-14-UTP, BODIPY® TMR-14-UTP, BODIPY® TR-14-UTP, Rhodamine Green™-5-UTP, Alexa Fluor® 488-5-UTP, Alexa Fluor® 546-14-UTP (Molecular Probes, Inc. Eugene, OR, USA). One may also custom synthesize nucleotides having other fluorophores. *See Henegariu et al., Nature Biotechnol.* 18: 345-348 (2000), the disclosure of which is incorporated herein by reference in its entirety.

Haptens that are commonly conjugated to nucleotides for subsequent labeling include biotin (biotin-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA; biotin-21-UTP, biotin-21-dUTP, Clontech Laboratories, Inc., Palo Alto, CA, USA), digoxigenin (DIG-11-dUTP, alkali labile, DIG-11-UTP, Roche Diagnostics Corp., Indianapolis, IN, USA), and dinitrophenyl (dinitrophenyl-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA).

Nucleic acid molecules can be labeled by incorporation of labeled nucleotide analogues into the nucleic acid. Such analogues can be incorporated by enzymatic polymerization, such as by nick translation, random priming, polymerase chain reaction (PCR), terminal transferase tailing, and end-filling of overhangs, for DNA molecules, and *in vitro* transcription driven, *e.g.*, from phage promoters, such as T7, T3, and SP6, for RNA molecules. Commercial kits are readily available for each such labeling approach. Analogues can also be incorporated during automated solid phase chemical synthesis. Labels can also be incorporated after nucleic acid synthesis, with the 5' phosphate and 3' hydroxyl providing convenient sites for post-synthetic covalent attachment of detectable labels.

Other post-synthetic approaches also permit internal labeling of nucleic acids. For example, fluorophores can be attached using a cisplatin reagent that reacts with the N7 of guanine residues (and, to a lesser extent, adenine bases) in DNA, RNA, and PNA to provide a stable coordination complex between the nucleic acid and fluorophore label
5 (Universal Linkage System) (available from Molecular Probes, Inc., Eugene, OR, USA and Amersham Pharmacia Biotech, Piscataway, NJ, USA); *see Alers et al., Genes, Chromosomes & Cancer* 25: 301-305 (1999); Jelsma *et al., J. NIH Res.* 5: 82 (1994); Van Belkum *et al., BioTechniques* 16: 148-153 (1994), incorporated herein by reference. As another example, nucleic acids can be labeled using a disulfide-containing linker
10 (FastTag™ Reagent, Vector Laboratories, Inc., Burlingame, CA, USA) that is photo- or thermally-coupled to the target nucleic acid using aryl azide chemistry; after reduction, a free thiol is available for coupling to a hapten, fluorophore, sugar, affinity ligand, or other marker.

One or more independent or interacting labels can be incorporated into the
15 nucleic acid molecules of the present invention. For example, both a fluorophore and a moiety that in proximity thereto acts to quench fluorescence can be included to report specific hybridization through release of fluorescence quenching or to report exonucleotidic excision. *See, e.g., Tyagi et al., Nature Biotechnol.* 14: 303-308 (1996); Tyagi *et al., Nature Biotechnol.* 16: 49-53 (1998); Sokol *et al., Proc. Natl. Acad. Sci.*
20 *USA* 95: 11538-11543 (1998); Kostrikis *et al., Science* 279: 1228-1229 (1998); Marras *et al., Genet. Anal.* 14: 151-156 (1999); U. S. Patent 5,846,726; 5,925,517; 5,925,517; 5,723,591 and 5,538,848; Holland *et al., Proc. Natl. Acad. Sci. USA* 88: 7276-7280 (1991); Heid *et al., Genome Res.* 6(10): 986-94 (1996); Kuimelis *et al., Nucleic Acids Symp. Ser.* (37): 255-6 (1997); the disclosures of which are incorporated herein by
25 reference in their entireties.

Nucleic acid molecules of the invention may be modified by altering one or more native phosphodiester internucleoside bonds to more nuclease-resistant, internucleoside bonds. *See Hartmann et al. (eds.), Manual of Antisense Methodology: Perspectives in*
30 *Antisense Science*, Kluwer Law International (1999); Stein *et al. (eds.), Applied Antisense Oligonucleotide Technology*, Wiley-Liss (1998); Chadwick *et al. (eds.), Oligonucleotides as Therapeutic Agents - Symposium No. 209*, John Wiley & Son Ltd (1997); the disclosures of which are incorporated herein by reference in their entireties.

Such altered internucleoside bonds are often desired for antisense techniques or for targeted gene correction. *See Gamper et al., Nucl. Acids Res.* 28(21): 4332-4339 (2000), the disclosure of which is incorporated herein by reference in its entirety.

Modified oligonucleotide backbones include, without limitation,
5 phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having
10 normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Representative United States patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U. S. Patents 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019;
15 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050, the disclosures of which are incorporated herein by reference in their entireties. In a preferred embodiment, the modified internucleoside linkages may be used for antisense techniques.

20 Other modified oligonucleotide backbones do not include a phosphorus atom, but have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a
25 nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts. Representative U.S. patents
30 that teach the preparation of the above backbones include, but are not limited to, U.S. Patent 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307;

5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437 and 5,677,439; the disclosures of which are incorporated herein by reference in their entireties.

In other preferred oligonucleotide mimetics, both the sugar and the internucleoside linkage are replaced with novel groups, such as peptide nucleic acids (PNA). In PNA compounds, the phosphodiester backbone of the nucleic acid is replaced with an amide-containing backbone, in particular by repeating N-(2-aminoethyl) glycine units linked by amide bonds. Nucleobases are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone, typically by methylene carbonyl linkages. PNA can be synthesized using a modified peptide synthesis protocol. PNA oligomers can be synthesized by both Fmoc and tBoc methods. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Automated PNA synthesis is readily achievable on commercial synthesizers (see, e.g., "PNA User's Guide," Rev. 2, February 1998, Perseptive Biosystems Part No. 60138, Applied Biosystems, Inc., Foster City, CA).

PNA molecules are advantageous for a number of reasons. First, because the PNA backbone is uncharged, PNA/DNA and PNA/RNA duplexes have a higher thermal stability than is found in DNA/DNA and DNA/RNA duplexes. The T_m of a PNA/DNA or PNA/RNA duplex is generally 1°C higher per base pair than the T_m of the corresponding DNA/DNA or DNA/RNA duplex (in 100 mM NaCl). Second, PNA molecules can also form stable PNA/DNA complexes at low ionic strength, under conditions in which DNA/DNA duplex formation does not occur. Third, PNA also demonstrates greater specificity in binding to complementary DNA because a PNA/DNA mismatch is more destabilizing than DNA/DNA mismatch. A single mismatch in mixed a PNA/DNA 15-mer lowers the T_m by 8–20°C (15°C on average). In the corresponding DNA/DNA duplexes, a single mismatch lowers the T_m by 4–16°C (11°C on average). Because PNA probes can be significantly shorter than DNA probes, their specificity is greater. Fourth, PNA oligomers are resistant to degradation by enzymes, and the lifetime of these compounds is extended both *in vivo* and *in vitro* because nucleases and proteases do not recognize the PNA polyamide backbone with nucleobase sidechains. See, e.g., Ray *et al.*, *FASEB J.* 14(9): 1041-60 (2000); Nielsen *et al.*, *Pharmacol Toxicol.* 86(1):

3-7 (2000); Larsen *et al.*, *Biochim Biophys Acta*. 1489(1): 159-66 (1999); Nielsen, *Curr. Opin. Struct. Biol.* 9(3): 353-7 (1999), and Nielsen, *Curr. Opin. Biotechnol.* 10(1): 71-5 (1999), the disclosures of which are incorporated herein by reference in their entireties.

Nucleic acid molecules may be modified compared to their native structure
5 throughout the length of the nucleic acid molecule or can be localized to discrete portions thereof. As an example of the latter, chimeric nucleic acids can be synthesized that have discrete DNA and RNA domains and that can be used for targeted gene repair and modified PCR reactions, as further described in U.S. Patents 5,760,012 and 5,731,181, Misra *et al.*, *Biochem.* 37: 1917-1925 (1998); and Finn *et al.*, *Nucl. Acids Res.* 24:
10 3357-3363 (1996), the disclosures of which are incorporated herein by reference in their entireties.

Unless otherwise specified, nucleic acids of the present invention can include any topological conformation appropriate to the desired use; the term thus explicitly comprehends, among others, single-stranded, double-stranded, triplexed, quadruplexed,
15 partially double-stranded, partially-triplexed, partially-quadruplexed, branched, hairpinned, circular, and padlocked conformations. Padlock conformations and their utilities are further described in Banér *et al.*, *Curr. Opin. Biotechnol.* 12: 11-15 (2001); Escude *et al.*, *Proc. Natl. Acad. Sci. USA* 14: 96(19):10603-7 (1999); Nilsson *et al.*, *Science* 265(5181): 2085-8 (1994), the disclosures of which are incorporated herein by
20 reference in their entireties. Triplex and quadruplex conformations, and their utilities, are reviewed in Praseuth *et al.*, *Biochim. Biophys. Acta*. 1489(1): 181-206 (1999); Fox, *Curr. Med. Chem.* 7(1): 17-37 (2000); Kochetkova *et al.*, *Methods Mol. Biol.* 130: 189-201 (2000); Chan *et al.*, *J. Mol. Med.* 75(4): 267-82 (1997), the disclosures of which are incorporated herein by reference in their entireties.

25

Methods for Using Nucleic Acid Molecules as Probes and Primers

The isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize, and quantify hybridizing nucleic acids in, and isolate hybridizing nucleic acids from, both genomic and transcript-derived nucleic
30 acid samples. When free in solution, such probes are typically, but not invariably, detectably labeled; bound to a substrate, as in a microarray, such probes are typically, but not invariably unlabeled.

In one embodiment, the isolated nucleic acids of the present invention can be used as probes to detect and characterize gross alterations in the gene of a BSNA, such as deletions, insertions, translocations, and duplications of the BSNA genomic locus through fluorescence *in situ* hybridization (FISH) to chromosome spreads. *See, e.g.,* Andreeff *et al.* (eds.), Introduction to Fluorescence *In Situ* Hybridization: Principles and Clinical Applications, John Wiley & Sons (1999), the disclosure of which is incorporated herein by reference in its entirety. The isolated nucleic acids of the present invention can be used as probes to assess smaller genomic alterations using, *e.g.*, Southern blot detection of restriction fragment length polymorphisms. The isolated nucleic acid molecules of the present invention can be used as probes to isolate genomic clones that include the nucleic acid molecules of the present invention, which thereafter can be restriction mapped and sequenced to identify deletions, insertions, translocations, and substitutions (single nucleotide polymorphisms, SNPs) at the sequence level.

In another embodiment, the isolated nucleic acid molecules of the present invention can be used as probes to detect, characterize, and quantify BSNA in, and isolate BSNA from, transcript-derived nucleic acid samples. In one aspect, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by length, and quantify mRNA by Northern blot of total or poly-A⁺-selected RNA samples. In another aspect, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by location, and quantify mRNA by *in situ* hybridization to tissue sections. *See, e.g.,* Schwarczacher *et al.*, In Situ Hybridization, Springer-Verlag New York (2000), the disclosure of which is incorporated herein by reference in its entirety. In another preferred embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to measure the representation of clones in a cDNA library or to isolate hybridizing nucleic acid molecules acids from cDNA libraries, permitting sequence level characterization of mRNAs that hybridize to BSNAs, including, without limitations, identification of deletions, insertions, substitutions, truncations, alternatively spliced forms and single nucleotide polymorphisms. In yet another preferred embodiment, the nucleic acid molecules of the instant invention may be used in microarrays.

All of the aforementioned probe techniques are well within the skill in the art, and are described at greater length in standard texts such as Sambrook (2001), *supra*;

Ausubel (1999), *supra*; and Walker *et al.* (eds.), The Nucleic Acids Protocols Handbook, Humana Press (2000), the disclosures of which are incorporated herein by reference in their entirety.

Thus, in one embodiment, a nucleic acid molecule of the invention may be used
5 as a probe or primer to identify or amplify a second nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of the invention. In a preferred embodiment, the probe or primer is derived from a nucleic acid molecule encoding a BSP. In a more preferred embodiment, the probe or primer is derived from a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 165 through 280.
10 In another preferred embodiment, the probe or primer is derived from a BSNA. In a more preferred embodiment, the probe or primer is derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1 through 164.

In general, a probe or primer is at least 10 nucleotides in length, more preferably at least 12, more preferably at least 14 and even more preferably at least 16 or 17
15 nucleotides in length. In an even more preferred embodiment, the probe or primer is at least 18 nucleotides in length, even more preferably at least 20 nucleotides and even more preferably at least 22 nucleotides in length. Primers and probes may also be longer in length. For instance, a probe or primer may be 25 nucleotides in length, or may be 30, 40 or 50 nucleotides in length. Methods of performing nucleic acid hybridization using
20 oligonucleotide probes are well-known in the art. *See, e.g.*, Sambrook *et al.*, 1989, *supra*, Chapter 11 and pp. 11.31-11.32 and 11.40-11.44, which describes radiolabeling of short probes, and pp. 11.45-11.53, which describe hybridization conditions for oligonucleotide probes, including specific conditions for probe hybridization (pp. 11.50-11.51).

Methods of performing primer-directed amplification are also well-known in the
25 art. Methods for performing the polymerase chain reaction (PCR) are compiled, *inter alia*, in McPherson, PCR Basics: From Background to Bench, Springer Verlag (2000); Innis *et al.* (eds.), PCR Applications: Protocols for Functional Genomics, Academic Press (1999); Gelfand *et al.* (eds.), PCR Strategies, Academic Press (1998); Newton *et al.*, PCR, Springer-Verlag New York (1997); Burke (ed.), PCR: Essential Techniques,
30 John Wiley & Son Ltd (1996); White (ed.), PCR Cloning Protocols: From Molecular Cloning to Genetic Engineering, Vol. 67, Humana Press (1996); McPherson *et al.* (eds.), PCR 2: A Practical Approach, Oxford University Press, Inc. (1995); the disclosures of

which are incorporated herein by reference in their entireties. Methods for performing RT-PCR are collected, *e.g.*, in Siebert *et al.* (eds.), Gene Cloning and Analysis by RT-PCR, Eaton Publishing Company/Bio Techniques Books Division, 1998; Siebert (ed.), PCR Technique:RT-PCR, Eaton Publishing Company/ BioTechniques Books
5 (1995); the disclosure of which is incorporated herein by reference in its entirety.

PCR and hybridization methods may be used to identify and/or isolate allelic variants, homologous nucleic acid molecules and fragments of the nucleic acid molecules of the invention. PCR and hybridization methods may also be used to identify, amplify and/or isolate nucleic acid molecules that encode homologous proteins, analogs, fusion
10 protein or muteins of the invention. The nucleic acid primers of the present invention can be used to prime amplification of nucleic acid molecules of the invention, using transcript-derived or genomic DNA as template.

The nucleic acid primers of the present invention can also be used, for example, to prime single base extension (SBE) for SNP detection (*See, e.g.*, U.S. Patent 6,004,744,
15 the disclosure of which is incorporated herein by reference in its entirety).

Isothermal amplification approaches, such as rolling circle amplification, are also now well-described. *See, e.g.*, Schweitzer *et al.*, *Curr. Opin. Biotechnol.* 12(1): 21-7 (2001); U.S. Patents 5,854,033 and 5,714,320; and international patent publications WO 97/19193 and WO 00/15779, the disclosures of which are incorporated herein by
20 reference in their entireties. Rolling circle amplification can be combined with other techniques to facilitate SNP detection. *See, e.g.*, Lizardi *et al.*, *Nature Genet.* 19(3): 225-32 (1998).

Nucleic acid molecules of the present invention may be bound to a substrate either covalently or noncovalently. The substrate can be porous or solid, planar or non-
25 planar, unitary or distributed. The bound nucleic acid molecules may be used as hybridization probes, and may be labeled or unlabeled. In a preferred embodiment, the bound nucleic acid molecules are unlabeled.

In one embodiment, the nucleic acid molecule of the present invention is bound to a porous substrate, *e.g.*, a membrane, typically comprising nitrocellulose, nylon, or
30 positively-charged derivatized nylon. The nucleic acid molecule of the present invention can be used to detect a hybridizing nucleic acid molecule that is present within a labeled nucleic acid sample, *e.g.*, a sample of transcript-derived nucleic acids. In another

embodiment, the nucleic acid molecule is bound to a solid substrate, including, without limitation, glass, amorphous silicon, crystalline silicon or plastics. Examples of plastics include, without limitation, polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, polystyrene, polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, nitrocellulose, or mixtures thereof. The solid substrate may be any shape, including rectangular, disk-like and spherical. In a preferred embodiment, the solid substrate is a microscope slide or slide-shaped substrate.

The nucleic acid molecule of the present invention can be attached covalently to a surface of the support substrate or applied to a derivatized surface in a chaotropic agent that facilitates denaturation and adherence by presumed noncovalent interactions, or some combination thereof. The nucleic acid molecule of the present invention can be bound to a substrate to which a plurality of other nucleic acids are concurrently bound, hybridization to each of the plurality of bound nucleic acids being separately detectable. At low density, *e.g.* on a porous membrane, these substrate-bound collections are typically denominated macroarrays; at higher density, typically on a solid support, such as glass, these substrate bound collections of plural nucleic acids are colloquially termed microarrays. As used herein, the term microarray includes arrays of all densities. It is, therefore, another aspect of the invention to provide microarrays that include the nucleic acids of the present invention.

Expression Vectors, Host Cells and Recombinant Methods of Producing Polypeptides

Another aspect of the present invention relates to vectors that comprise one or more of the isolated nucleic acid molecules of the present invention, and host cells in which such vectors have been introduced.

The vectors can be used, *inter alia*, for propagating the nucleic acids of the present invention in host cells (cloning vectors), for shuttling the nucleic acids of the present invention between host cells derived from disparate organisms (shuttle vectors), for inserting the nucleic acids of the present invention into host cell chromosomes (insertion vectors), for expressing sense or antisense RNA transcripts of the nucleic acids of the present invention *in vitro* or within a host cell, and for expressing polypeptides encoded by the nucleic acids of the present invention, alone or as fusions to heterologous

polypeptides (expression vectors). Vectors of the present invention will often be suitable for several such uses.

Vectors are by now well-known in the art, and are described, *inter alia*, in Jones *et al.* (eds.), Vectors: Cloning Applications: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Jones *et al.* (eds.), Vectors: Expression Systems: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Gacesa *et al.*, Vectors: Essential Data, John Wiley & Sons Ltd. (1995); Cid-Arregui (eds.), Viral Vectors: Basic Science and Gene Therapy, Eaton Publishing Co. (2000); Sambrook (2001), *supra*; Ausubel (1999), *supra*; the disclosures of which are
10 incorporated herein by reference in their entireties. Furthermore, an enormous variety of vectors are available commercially. Use of existing vectors and modifications thereof being well within the skill in the art, only basic features need be described here.

Nucleic acid sequences may be expressed by operatively linking them to an expression control sequence in an appropriate expression vector and employing that
15 expression vector to transform an appropriate unicellular host. Expression control sequences are sequences which control the transcription, post-transcriptional events and translation of nucleic acid sequences. Such operative linking of a nucleic sequence of this invention to an expression control sequence, of course, includes, if not already part of the nucleic acid sequence, the provision of a translation initiation codon, ATG or
20 GTG, in the correct reading frame upstream of the nucleic acid sequence.

A wide variety of host/expression vector combinations may be employed in expressing the nucleic acid sequences of this invention. Useful expression vectors, for example, may consist of segments of chromosomal, non-chromosomal and synthetic nucleic acid sequences.

25 In one embodiment, prokaryotic cells may be used with an appropriate vector. Prokaryotic host cells are often used for cloning and expression. In a preferred embodiment, prokaryotic host cells include *E. coli*, *Pseudomonas*, *Bacillus* and *Streptomyces*. In a preferred embodiment, bacterial host cells are used to express the nucleic acid molecules of the instant invention. Useful expression vectors for bacterial
30 hosts include bacterial plasmids, such as those from *E. coli*, *Bacillus* or *Streptomyces*, including pBluescript, pGEX-2T, pUC vectors, col E1, pCR1, pBR322, pMB9 and their derivatives, wider host range plasmids, such as RP4, phage DNAs, *e.g.*, the numerous

derivatives of phage lambda, *e.g.*, NM989, λ GT10 and λ GT11, and other phages, *e.g.*, M13 and filamentous single-stranded phage DNA. Where *E. coli* is used as host, selectable markers are, analogously, chosen for selectivity in gram negative bacteria: *e.g.*, typical markers confer resistance to antibiotics, such as ampicillin, tetracycline, chloramphenicol, kanamycin, streptomycin and zeocin; auxotrophic markers can also be used.

In other embodiments, eukaryotic host cells, such as yeast, insect, mammalian or plant cells, may be used. Yeast cells, typically *S. cerevisiae*, are useful for eukaryotic genetic studies, due to the ease of targeting genetic changes by homologous recombination and the ability to easily complement genetic defects using recombinantly expressed proteins. Yeast cells are useful for identifying interacting protein components, *e.g.* through use of a two-hybrid system. In a preferred embodiment, yeast cells are useful for protein expression. Vectors of the present invention for use in yeast will typically, but not invariably, contain an origin of replication suitable for use in yeast and a selectable marker that is functional in yeast. Yeast vectors include Yeast Integrating plasmids (*e.g.*, YIp5) and Yeast Replicating plasmids (the YRp and YEplac series plasmids), Yeast Centromere plasmids (the YCp series plasmids), Yeast Artificial Chromosomes (YACs) which are based on yeast linear plasmids, denoted YLp, pGPD-2, 2 μ plasmids and derivatives thereof, and improved shuttle vectors such as those described in Gietz *et al.*, *Gene*, 74: 527-34 (1988) (YIplac, YEplac and YCplac). Selectable markers in yeast vectors include a variety of auxotrophic markers, the most common of which are (in *Saccharomyces cerevisiae*) URA3, HIS3, LEU2, TRP1 and LYS2, which complement specific auxotrophic mutations, such as *ura3-52*, *his3-D1*, *leu2-D1*, *trp1-D1* and *lys2-201*.

Insect cells are often chosen for high efficiency protein expression. Where the host cells are from *Spodoptera frugiperda*, *e.g.*, Sf9 and Sf21 cell lines, and expresSFTM cells (Protein Sciences Corp., Meriden, CT, USA)), the vector replicative strategy is typically based upon the baculovirus life cycle. Typically, baculovirus transfer vectors are used to replace the wild-type AcMNPV polyhedrin gene with a heterologous gene of interest. Sequences that flank the polyhedrin gene in the wild-type genome are positioned 5' and 3' of the expression cassette on the transfer vectors. Following co-transfection with AcMNPV DNA, a homologous recombination event occurs between

these sequences resulting in a recombinant virus carrying the gene of interest and the polyhedrin or p10 promoter. Selection can be based upon visual screening for lacZ fusion activity.

In another embodiment, the host cells may be mammalian cells, which are particularly useful for expression of proteins intended as pharmaceutical agents, and for screening of potential agonists and antagonists of a protein or a physiological pathway. Mammalian vectors intended for autonomous extrachromosomal replication will typically include a viral origin, such as the SV40 origin (for replication in cell lines expressing the large T-antigen, such as COS1 and COS7 cells), the papillomavirus origin, or the EBV origin for long term episomal replication (for use, *e.g.*, in 293-EBNA cells, which constitutively express the EBV EBNA-1 gene product and adenovirus E1A). Vectors intended for integration, and thus replication as part of the mammalian chromosome, can, but need not, include an origin of replication functional in mammalian cells, such as the SV40 origin. Vectors based upon viruses, such as adenovirus, adeno-associated virus, vaccinia virus, and various mammalian retroviruses, will typically replicate according to the viral replicative strategy. Selectable markers for use in mammalian cells include resistance to neomycin (G418), blasticidin, hygromycin and to zeocin, and selection based upon the purine salvage pathway using HAT medium.

Expression in mammalian cells can be achieved using a variety of plasmids, including pSV2, pBC12BI, and p91023, as well as lytic virus vectors (*e.g.*, vaccinia virus, adeno virus, and baculovirus), episomal virus vectors (*e.g.*, bovine papillomavirus), and retroviral vectors (*e.g.*, murine retroviruses). Useful vectors for insect cells include baculoviral vectors and pVL 941.

Plant cells can also be used for expression, with the vector replicon typically derived from a plant virus (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) and selectable markers chosen for suitability in plants.

It is known that codon usage of different host cells may be different. For example, a plant cell and a human cell may exhibit a difference in codon preference for encoding a particular amino acid. As a result, human mRNA may not be efficiently translated in a plant, bacteria or insect host cell. Therefore, another embodiment of this invention is directed to codon optimization. The codons of the nucleic acid molecules of the invention may be modified to resemble, as much as possible, genes naturally

contained within the host cell without altering the amino acid sequence encoded by the nucleic acid molecule.

Any of a wide variety of expression control sequences may be used in these vectors to express the DNA sequences of this invention. Such useful expression control sequences include the expression control sequences associated with structural genes of the foregoing expression vectors. Expression control sequences that control transcription include, *e.g.*, promoters, enhancers and transcription termination sites. Expression control sequences in eukaryotic cells that control post-transcriptional events include splice donor and acceptor sites and sequences that modify the half-life of the transcribed RNA, *e.g.*, sequences that direct poly(A) addition or binding sites for RNA-binding proteins. Expression control sequences that control translation include ribosome binding sites, sequences which direct targeted expression of the polypeptide to or within particular cellular compartments, and sequences in the 5' and 3' untranslated regions that modify the rate or efficiency of translation.

Examples of useful expression control sequences for a prokaryote, *e.g.*, *E. coli*, will include a promoter, often a phage promoter, such as phage lambda pL promoter, the *trc* promoter, a hybrid derived from the *trp* and *lac* promoters, the bacteriophage T7 promoter (in *E. coli* cells engineered to express the T7 polymerase), the TAC or TRC system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, or the *araBAD* operon. Prokaryotic expression vectors may further include transcription terminators, such as the *aspA* terminator, and elements that facilitate translation, such as a consensus ribosome binding site and translation termination codon, Schomer *et al.*, *Proc. Natl. Acad. Sci. USA* 83: 8506-8510 (1986).

Expression control sequences for yeast cells, typically *S. cerevisiae*, will include a yeast promoter, such as the *CYC1* promoter, the *GAL1* promoter, the *GAL10* promoter, *ADH1* promoter, the promoters of the yeast α -mating system, or the *GPD* promoter, and will typically have elements that facilitate transcription termination, such as the transcription termination signals from the *CYC1* or *ADH1* gene.

Expression vectors useful for expressing proteins in mammalian cells will include a promoter active in mammalian cells. These promoters include those derived from mammalian viruses, such as the enhancer-promoter sequences from the immediate early gene of the human cytomegalovirus (CMV), the enhancer-promoter sequences from the

Rous sarcoma virus long terminal repeat (RSV LTR), the enhancer-promoter from SV40 or the early and late promoters of adenovirus. Other expression control sequences include the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase. Other expression control sequences include those from
5 the gene comprising the BSNA of interest. Often, expression is enhanced by incorporation of polyadenylation sites, such as the late SV40 polyadenylation site and the polyadenylation signal and transcription termination sequences from the bovine growth hormone (BGH) gene, and ribosome binding sites. Furthermore, vectors can include introns, such as intron II of rabbit β -globin gene and the SV40 splice elements.

10 Preferred nucleic acid vectors also include a selectable or amplifiable marker gene and means for amplifying the copy number of the gene of interest. Such marker genes are well-known in the art. Nucleic acid vectors may also comprise stabilizing sequences (*e.g.*, ori- or ARS-like sequences and telomere-like sequences), or may alternatively be designed to favor directed or non-directed integration into the host cell
15 genome. In a preferred embodiment, nucleic acid sequences of this invention are inserted in frame into an expression vector that allows high level expression of an RNA which encodes a protein comprising the encoded nucleic acid sequence of interest. Nucleic acid cloning and sequencing methods are well-known to those of skill in the art and are described in an assortment of laboratory manuals, including Sambrook (1989), *supra*,
20 Sambrook (2000), *supra*; and Ausubel (1992), *supra*, Ausubel (1999), *supra*. Product information from manufacturers of biological, chemical and immunological reagents also provide useful information.

Expression vectors may be either constitutive or inducible. Inducible vectors include either naturally inducible promoters, such as the trc promoter, which is regulated
25 by the lac operon, and the pL promoter, which is regulated by tryptophan, the MMTV-LTR promoter, which is inducible by dexamethasone, or can contain synthetic promoters and/or additional elements that confer inducible control on adjacent promoters. Examples of inducible synthetic promoters are the hybrid Plac/ara-1 promoter and the PLtetO-1 promoter. The PLtetO-1 promoter takes advantage of the high expression levels
30 from the PL promoter of phage lambda, but replaces the lambda repressor sites with two copies of operator 2 of the Tn10 tetracycline resistance operon, causing this promoter to be tightly repressed by the Tet repressor protein and induced in response to tetracycline

-50-

(Tc) and Tc derivatives such as anhydrotetracycline. Vectors may also be inducible because they contain hormone response elements, such as the glucocorticoid response element (GRE) and the estrogen response element (ERE), which can confer hormone inducibility where vectors are used for expression in cells having the respective hormone
5 receptors. To reduce background levels of expression, elements responsive to ecdysone, an insect hormone, can be used instead, with coexpression of the ecdysone receptor.

In one aspect of the invention, expression vectors can be designed to fuse the expressed polypeptide to small protein tags that facilitate purification and/or visualization. Tags that facilitate purification include a polyhistidine tag that facilitates
10 purification of the fusion protein by immobilized metal affinity chromatography, for example using NiNTA resin (Qiagen Inc., Valencia, CA, USA) or TALON™ resin (cobalt immobilized affinity chromatography medium, Clontech Labs, Palo Alto, CA, USA). The fusion protein can include a chitin-binding tag and self-excising intein, permitting chitin-based purification with self-removal of the fused tag (IMPACT™
15 system, New England Biolabs, Inc., Beverly, MA, USA). Alternatively, the fusion protein can include a calmodulin-binding peptide tag, permitting purification by calmodulin affinity resin (Stratagene, La Jolla, CA, USA), or a specifically excisable fragment of the biotin carboxylase carrier protein, permitting purification of *in vivo* biotinylated protein using an avidin resin and subsequent tag removal (Promega,
20 Madison, WI, USA). As another useful alternative, the proteins of the present invention can be expressed as a fusion protein with glutathione-S-transferase, the affinity and specificity of binding to glutathione permitting purification using glutathione affinity resins, such as Glutathione-Superflow Resin (Clontech Laboratories, Palo Alto, CA, USA), with subsequent elution with free glutathione. Other tags include, for example,
25 the Xpress epitope, detectable by anti-Xpress antibody (Invitrogen, Carlsbad, CA, USA), a myc tag, detectable by anti-myc tag antibody, the V5 epitope, detectable by anti-V5 antibody (Invitrogen, Carlsbad, CA, USA), FLAG® epitope, detectable by anti-FLAG® antibody (Stratagene, La Jolla, CA, USA), and the HA epitope.

For secretion of expressed proteins, vectors can include appropriate sequences
30 that encode secretion signals, such as leader peptides. For example, the pSecTag2 vectors (Invitrogen, Carlsbad, CA, USA) are 5.2 kb mammalian expression vectors that

carry the secretion signal from the V-J2-C region of the mouse Ig kappa-chain for efficient secretion of recombinant proteins from a variety of mammalian cell lines.

Expression vectors can also be designed to fuse proteins encoded by the heterologous nucleic acid insert to polypeptides that are larger than purification and/or
5 identification tags. Useful fusion proteins include those that permit display of the encoded protein on the surface of a phage or cell, fusion to intrinsically fluorescent proteins, such as those that have a green fluorescent protein (GFP)-like chromophore, fusions to the IgG Fc region, and fusion proteins for use in two hybrid systems.

Vectors for phage display fuse the encoded polypeptide to, *e.g.*, the gene III
10 protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13. *See* Barbas *et al.*, Phage Display: A Laboratory Manual, Cold Spring Harbor Laboratory Press (2001); Kay *et al.* (eds.), Phage Display of Peptides and Proteins: A Laboratory Manual, Academic Press, Inc., (1996); Abelson *et al.* (eds.), Combinatorial Chemistry (Methods in Enzymology, Vol. 267) Academic Press (1996).
15 Vectors for yeast display, *e.g.* the pYD1 yeast display vector (Invitrogen, Carlsbad, CA, USA), use the α -agglutinin yeast adhesion receptor to display recombinant protein on the surface of *S. cerevisiae*. Vectors for mammalian display, *e.g.*, the pDisplay™ vector (Invitrogen, Carlsbad, CA, USA), target recombinant proteins using an N-terminal cell surface targeting signal and a C-terminal transmembrane anchoring domain of platelet
20 derived growth factor receptor.

A wide variety of vectors now exist that fuse proteins encoded by heterologous nucleic acids to the chromophore of the substrate-independent, intrinsically fluorescent green fluorescent protein from *Aequorea victoria* ("GFP") and its variants. The GFP-like chromophore can be selected from GFP-like chromophores found in naturally occurring
25 proteins, such as *A. victoria* GFP (GenBank accession number AAA27721), *Renilla reniformis* GFP, FP583 (GenBank accession no. AF168419) (DsRed), FP593 (AF272711), FP483 (AF168420), FP484 (AF168424), FP595 (AF246709), FP486 (AF168421), FP538 (AF168423), and FP506 (AF168422), and need include only so much of the native protein as is needed to retain the chromophore's intrinsic
30 fluorescence. Methods for determining the minimal domain required for fluorescence are known in the art. *See* Li *et al.*, *J. Biol. Chem.* 272: 28545-28549 (1997). Alternatively, the GFP-like chromophore can be selected from GFP-like chromophores modified from

those found in nature. The methods for engineering such modified GFP-like chromophores and testing them for fluorescence activity, both alone and as part of protein fusions, are well-known in the art. See Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996) and Palm *et al.*, *Methods Enzymol.* 302: 378-394 (1999), incorporated herein by reference in its entirety. A variety of such modified chromophores are now commercially available and can readily be used in the fusion proteins of the present invention. These include EGFP ("enhanced GFP"), EBFP ("enhanced blue fluorescent protein"), BFP2, EYFP ("enhanced yellow fluorescent protein"), ECFP ("enhanced cyan fluorescent protein") or Citrine. EGFP (*see, e.g.*, Cormack *et al.*, *Gene* 173: 33-38 (1996); United States Patent Nos. 6,090,919 and 5,804,387) is found on a variety of vectors, both plasmid and viral, which are available commercially (Clontech Labs, Palo Alto, CA, USA); EBFP is optimized for expression in mammalian cells whereas BFP2, which retains the original jellyfish codons, can be expressed in bacteria (*see, e.g.*, Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996) and Cormack *et al.*, *Gene* 173: 33-38 (1996)). Vectors containing these blue-shifted variants are available from Clontech Labs (Palo Alto, CA, USA). Vectors containing EYFP, ECFP (*see, e.g.*, Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996); Miyawaki *et al.*, *Nature* 388: 882-887 (1997)) and Citrine (*see, e.g.*, Heikal *et al.*, *Proc. Natl. Acad. Sci. USA* 97: 11996-12001 (2000)) are also available from Clontech Labs. The GFP-like chromophore can also be drawn from other modified GFPs, including those described in U.S. Patents 6,124,128; 6,096,865; 6,090,919; 6,066,476; 6,054,321; 6,027,881; 5,968,750; 5,874,304; 5,804,387; 5,777,079; 5,741,668; and 5,625,048, the disclosures of which are incorporated herein by reference in their entireties. See also Conn (ed.), Green Fluorescent Protein (Methods in Enzymology, Vol. 302), Academic Press, Inc. (1999). The GFP-like chromophore of each of these GFP variants can usefully be included in the fusion proteins of the present invention.

Fusions to the IgG Fc region increase serum half life of protein pharmaceutical products through interaction with the FcRn receptor (also denominated the FcRp receptor and the Brambell receptor, FcRb), further described in International Patent Application Nos. WO 97/43316, WO 97/34631, WO 96/32478, WO 96/18412.

For long-term, high-yield recombinant production of the proteins, protein fusions, and protein fragments of the present invention, stable expression is preferred. Stable

expression is readily achieved by integration into the host cell genome of vectors having selectable markers, followed by selection of these integrants. Vectors such as pUB6/V5-His A, B, and C (Invitrogen, Carlsbad, CA, USA) are designed for high-level stable expression of heterologous proteins in a wide range of mammalian tissue types and cell lines. pUB6/V5-His uses the promoter/enhancer sequence from the human ubiquitin C gene to drive expression of recombinant proteins: expression levels in 293, CHO, and NIH3T3 cells are comparable to levels from the CMV and human EF-1a promoters. The bsd gene permits rapid selection of stably transfected mammalian cells with the potent antibiotic blasticidin.

10 Replication incompetent retroviral vectors, typically derived from Moloney murine leukemia virus, also are useful for creating stable transfectants having integrated provirus. The highly efficient transduction machinery of retroviruses, coupled with the availability of a variety of packaging cell lines such as RetroPack™ PT 67, EcoPack2™-293, AmphoPack-293, and GP2-293 cell lines (all available from Clontech Laboratories, Palo Alto, CA, USA), allow a wide host range to be infected with high efficiency; 15 varying the multiplicity of infection readily adjusts the copy number of the integrated provirus.

Of course, not all vectors and expression control sequences will function equally well to express the nucleic acid sequences of this invention. Neither will all hosts 20 function equally well with the same expression system. However, one of skill in the art may make a selection among these vectors, expression control sequences and hosts without undue experimentation and without departing from the scope of this invention. For example, in selecting a vector, the host must be considered because the vector must be replicated in it. The vector's copy number, the ability to control that copy number, the 25 ability to control integration, if any, and the expression of any other proteins encoded by the vector, such as antibiotic or other selection markers, should also be considered. The present invention further includes host cells comprising the vectors of the present invention, either present episomally within the cell or integrated, in whole or in part, into the host cell chromosome. Among other considerations, some of which are described 30 above, a host cell strain may be chosen for its ability to process the expressed protein in the desired fashion. Such post-translational modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation,

and acylation, and it is an aspect of the present invention to provide BSPs with such post-translational modifications.

Polypeptides of the invention may be post-translationally modified. Post-translational modifications include phosphorylation of amino acid residues serine, threonine and/or tyrosine, N-linked and/or O-linked glycosylation, methylation, acetylation, prenylation, methylation, acetylation, arginylation, ubiquitination and racemization. One may determine whether a polypeptide of the invention is likely to be post-translationally modified by analyzing the sequence of the polypeptide to determine if there are peptide motifs indicative of sites for post-translational modification. There are a number of computer programs that permit prediction of post-translational modifications. See, e.g., www.expasy.org (accessed August 31, 2001), which includes PSORT, for prediction of protein sorting signals and localization sites, SignalP, for prediction of signal peptide cleavage sites, MITOPROT and Predotar, for prediction of mitochondrial targeting sequences, NetOGlyc, for prediction of type O-glycosylation sites in mammalian proteins, big-PI Predictor and DGPI, for prediction of prenylation-anchor and cleavage sites, and NetPhos, for prediction of Ser, Thr and Tyr phosphorylation sites in eukaryotic proteins. Other computer programs, such as those included in GCG, also may be used to determine post-translational modification peptide motifs.

General examples of types of post-translational modifications may be found in web sites such as the Delta Mass database <http://www.abrf.org/ABRF/ResearchCommittees/deltamass/deltamass.html> (accessed October 19, 2001); "GlycoSuiteDB: a new curated relational database of glycoprotein glycan structures and their biological sources" Cooper et al. *Nucleic Acids Res.* 29; 332-335 (2001) and <http://www.glycosuite.com/> (accessed October 19, 2001); "O-GLYCBASE version 4.0: a revised database of O-glycosylated proteins" Gupta et al. *Nucleic Acids Research*, 27: 370-372 (1999) and <http://www.cbs.dtu.dk/databases/OGLYCBASE/> (accessed October 19, 2001); "PhosphoBase, a database of phosphorylation sites: release 2.0.", Kreegipuu et al. *Nucleic Acids Res* 27(1):237-239 (1999) and <http://www.cbs.dtu.dk/databases/PhosphoBase/> (accessed October 19, 2001); or <http://pir.georgetown.edu/pirwww/search/textresid.html> (accessed October 19, 2001).

Tumorigenesis is often accompanied by alterations in the post-translational modifications of proteins. Thus, in another embodiment, the invention provides polypeptides from cancerous cells or tissues that have altered post-translational modifications compared to the post-translational modifications of polypeptides from normal cells or tissues. A number of altered post-translational modifications are known. One common alteration is a change in phosphorylation state, wherein the polypeptide from the cancerous cell or tissue is hyperphosphorylated or hypophosphorylated compared to the polypeptide from a normal tissue, or wherein the polypeptide is phosphorylated on different residues than the polypeptide from a normal cell. Another common alteration is a change in glycosylation state, wherein the polypeptide from the cancerous cell or tissue has more or less glycosylation than the polypeptide from a normal tissue, and/or wherein the polypeptide from the cancerous cell or tissue has a different type of glycosylation than the polypeptide from a noncancerous cell or tissue. Changes in glycosylation may be critical because carbohydrate-protein and carbohydrate-carbohydrate interactions are important in cancer cell progression, dissemination and invasion. See, e.g., Barchi, *Curr. Pharm. Des.* 6: 485-501 (2000), Verma, *Cancer Biochem. Biophys.* 14: 151-162 (1994) and Dennis et al., *Bioessays* 5: 412-421 (1999).

Another post-translational modification that may be altered in cancer cells is prenylation. Prenylation is the covalent attachment of a hydrophobic prenyl group (either farnesyl or geranylgeranyl) to a polypeptide. Prenylation is required for localizing a protein to a cell membrane and is often required for polypeptide function. For instance, the Ras superfamily of GTPase signaling proteins must be prenylated for function in a cell. See, e.g., Prendergast et al., *Semin. Cancer Biol.* 10: 443-452 (2000) and Khwaja et al., *Lancet* 355: 741-744 (2000).

Other post-translation modifications that may be altered in cancer cells include, without limitation, polypeptide methylation, acetylation, arginylation or racemization of amino acid residues. In these cases, the polypeptide from the cancerous cell may exhibit either increased or decreased amounts of the post-translational modification compared to the corresponding polypeptides from noncancerous cells.

Other polypeptide alterations in cancer cells include abnormal polypeptide cleavage of proteins and aberrant protein-protein interactions. Abnormal polypeptide cleavage may be cleavage of a polypeptide in a cancerous cell that does not usually occur

in a normal cell, or a lack of cleavage in a cancerous cell, wherein the polypeptide is cleaved in a normal cell. Aberrant protein-protein interactions may be either covalent cross-linking or non-covalent binding between proteins that do not normally bind to each other. Alternatively, in a cancerous cell, a protein may fail to bind to another protein to which it is bound in a noncancerous cell. Alterations in cleavage or in protein-protein interactions may be due to over- or underproduction of a polypeptide in a cancerous cell compared to that in a normal cell, or may be due to alterations in post-translational modifications (see above) of one or more proteins in the cancerous cell. See, e.g., Henschen-Edman, *Ann. N.Y. Acad. Sci.* 936: 580-593 (2001).

Alterations in polypeptide post-translational modifications, as well as changes in polypeptide cleavage and protein-protein interactions, may be determined by any method known in the art. For instance, alterations in phosphorylation may be determined by using anti-phosphoserine, anti-phosphothreonine or anti-phosphotyrosine antibodies or by amino acid analysis. Glycosylation alterations may be determined using antibodies specific for different sugar residues, by carbohydrate sequencing, or by alterations in the size of the glycoprotein, which can be determined by, e.g., SDS polyacrylamide gel electrophoresis (PAGE). Other alterations of post-translational modifications, such as prenylation, racemization, methylation, acetylation and arginylation, may be determined by chemical analysis, protein sequencing, amino acid analysis, or by using antibodies specific for the particular post-translational modifications. Changes in protein-protein interactions and in polypeptide cleavage may be analyzed by any method known in the art including, without limitation, non-denaturing PAGE (for non-covalent protein-protein interactions), SDS PAGE (for covalent protein-protein interactions and protein cleavage), chemical cleavage, protein sequencing or immunoassays.

In another embodiment, the invention provides polypeptides that have been post-translationally modified. In one embodiment, polypeptides may be modified enzymatically or chemically, by addition or removal of a post-translational modification. For example, a polypeptide may be glycosylated or deglycosylated enzymatically. Similarly, polypeptides may be phosphorylated using a purified kinase, such as a MAP kinase (e.g., p38, ERK, or JNK) or a tyrosine kinase (e.g., Src or erbB2). A polypeptide may also be modified through synthetic chemistry. Alternatively, one may isolate the polypeptide of interest from a cell or tissue that expresses the polypeptide with the

desired post-translational modification. In another embodiment, a nucleic acid molecule encoding the polypeptide of interest is introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide in the desired fashion. If the polypeptide does not contain a motif for a desired post-translational modification, one may alter the post-translational modification by mutating the nucleic acid sequence of a nucleic acid molecule encoding the polypeptide so that it contains a site for the desired post-translational modification. Amino acid sequences that may be post-translationally modified are known in the art. See, e.g., the programs described above on the website www.expasy.org. The nucleic acid molecule is then be introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide. Similarly, one may delete sites that are post-translationally modified by either mutating the nucleic acid sequence so that the encoded polypeptide does not contain the post-translational modification motif, or by introducing the native nucleic acid molecule into a host cell that is not capable of post-translationally modifying the encoded polypeptide.

In selecting an expression control sequence, a variety of factors should also be considered. These include, for example, the relative strength of the sequence, its controllability, and its compatibility with the nucleic acid sequence of this invention, particularly with regard to potential secondary structures. Unicellular hosts should be selected by consideration of their compatibility with the chosen vector, the toxicity of the product coded for by the nucleic acid sequences of this invention, their secretion characteristics, their ability to fold the polypeptide correctly, their fermentation or culture requirements, and the ease of purification from them of the products coded for by the nucleic acid sequences of this invention.

The recombinant nucleic acid molecules and more particularly, the expression vectors of this invention may be used to express the polypeptides of this invention as recombinant polypeptides in a heterologous host cell. The polypeptides of this invention may be full-length or less than full-length polypeptide fragments recombinantly expressed from the nucleic acid sequences according to this invention. Such polypeptides include analogs, derivatives and muteins that may or may not have biological activity.

Vectors of the present invention will also often include elements that permit *in vitro* transcription of RNA from the inserted heterologous nucleic acid. Such vectors

typically include a phage promoter, such as that from T7, T3, or SP6, flanking the nucleic acid insert. Often two different such promoters flank the inserted nucleic acid, permitting separate *in vitro* production of both sense and antisense strands.

Transformation and other methods of introducing nucleic acids into a host cell
5 (e.g., conjugation, protoplast transformation or fusion, transfection, electroporation, liposome delivery, membrane fusion techniques, high velocity DNA-coated pellets, viral infection and protoplast fusion) can be accomplished by a variety of methods which are well-known in the art (*See, for instance, Ausubel, supra, and Sambrook et al., supra*). Bacterial, yeast, plant or mammalian cells are transformed or transfected with an
10 expression vector, such as a plasmid, a cosmid, or the like, wherein the expression vector comprises the nucleic acid of interest. Alternatively, the cells may be infected by a viral expression vector comprising the nucleic acid of interest. Depending upon the host cell, vector, and method of transformation used, transient or stable expression of the polypeptide will be constitutive or inducible. One having ordinary skill in the art will be
15 able to decide whether to express a polypeptide transiently or stably, and whether to express the protein constitutively or inducibly.

A wide variety of unicellular host cells are useful in expressing the DNA sequences of this invention. These hosts may include well-known eukaryotic and prokaryotic hosts, such as strains of, fungi, yeast, insect cells such as *Spodoptera*
20 *frugiperda* (Sf9), animal cells such as CHO, as well as plant cells in tissue culture. Representative examples of appropriate host cells include, but are not limited to, bacterial cells, such as *E. coli*, *Caulobacter crescentus*, *Streptomyces* species, and *Salmonella typhimurium*; yeast cells, such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Pichia pastoris*, *Pichia methanolica*; insect cell lines, such as those from
25 *Spodoptera frugiperda*, e.g., Sf9 and Sf21 cell lines, and expresSF™ cells (Protein Sciences Corp., Meriden, CT, USA), *Drosophila* S2 cells, and *Trichoplusia ni* High Five® Cells (Invitrogen, Carlsbad, CA, USA); and mammalian cells. Typical mammalian cells include BHK cells, BSC 1 cells, BSC 40 cells, BMT 10 cells, VERO cells, COS1 cells, COS7 cells, Chinese hamster ovary (CHO) cells, 3T3 cells, NIH 3T3
30 cells, 293 cells, HEPG2 cells, HeLa cells, L cells, MDCK cells, HEK293 cells, WI38 cells, murine ES cell lines (e.g., from strains 129/SV, C57/BL6, DBA-1, 129/SVJ), K562 cells, Jurkat cells, and BW5147 cells. Other mammalian cell lines are well-known and

readily available from the American Type Culture Collection (ATCC) (Manassas, VA, USA) and the National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository at the Coriell Cell Repositories (Camden, NJ, USA). Cells or cell lines derived from breast are particularly preferred because they may provide a more native
5 post-translational processing. Particularly preferred are human breast cells.

Particular details of the transfection, expression and purification of recombinant proteins are well documented and are understood by those of skill in the art. Further details on the various technical aspects of each of the steps used in recombinant production of foreign genes in bacterial cell expression systems can be found in a number
10 of texts and laboratory manuals in the art. *See, e.g.,* Ausubel (1992), *supra*, Ausubel (1999), *supra*, Sambrook (1989), *supra*, and Sambrook (2001), *supra*, herein incorporated by reference.

Methods for introducing the vectors and nucleic acids of the present invention into the host cells are well-known in the art; the choice of technique will depend
15 primarily upon the specific vector to be introduced and the host cell chosen.

Nucleic acid molecules and vectors may be introduced into prokaryotes, such as *E. coli*, in a number of ways. For instance, phage lambda vectors will typically be packaged using a packaging extract (*e.g.,* Gigapack® packaging extract, Stratagene, La Jolla, CA, USA), and the packaged virus used to infect *E. coli*.

20 Plasmid vectors will typically be introduced into chemically competent or electrocompetent bacterial cells. *E. coli* cells can be rendered chemically competent by treatment, *e.g.,* with CaCl_2 , or a solution of Mg^{2+} , Mn^{2+} , Ca^{2+} , Rb^+ or K^+ , dimethyl sulfoxide, dithiothreitol, and hexamine cobalt (III), Hanahan, *J. Mol. Biol.* 166(4):557-80 (1983), and vectors introduced by heat shock. A wide variety of chemically competent
25 strains are also available commercially (*e.g.,* Epicurian Coli® XL10-Gold® Ultracompetent Cells (Stratagene, La Jolla, CA, USA); DH5 competent cells (Clontech Laboratories, Palo Alto, CA, USA); and TOP10 Chemically Competent *E. coli* Kit (Invitrogen, Carlsbad, CA, USA)). Bacterial cells can be rendered electrocompetent, that is, competent to take up exogenous DNA by electroporation, by various pre-pulse
30 treatments; vectors are introduced by electroporation followed by subsequent outgrowth in selected media. An extensive series of protocols is provided online in [Electroprotocols](#)

(BioRad, Richmond, CA, USA) (http://www.biorad.com/LifeScience/pdf/New_Gene_Pulser.pdf).

Vectors can be introduced into yeast cells by spheroplasting, treatment with lithium salts, electroporation, or protoplast fusion. Spheroplasts are prepared by the
5 action of hydrolytic enzymes such as snail-gut extract, usually denoted Glusulase, or Zymolyase, an enzyme from *Arthrobacter luteus*, to remove portions of the cell wall in the presence of osmotic stabilizers, typically 1 M sorbitol. DNA is added to the spheroplasts, and the mixture is co-precipitated with a solution of polyethylene glycol (PEG) and Ca^{2+} . Subsequently, the cells are resuspended in a solution of sorbitol, mixed
10 with molten agar and then layered on the surface of a selective plate containing sorbitol.

For lithium-mediated transformation, yeast cells are treated with lithium acetate, which apparently permeabilizes the cell wall, DNA is added and the cells are co-precipitated with PEG. The cells are exposed to a brief heat shock, washed free of PEG and lithium acetate, and subsequently spread on plates containing ordinary selective
15 medium. Increased frequencies of transformation are obtained by using specially-prepared single-stranded carrier DNA and certain organic solvents. Schiestl *et al.*, *Curr. Genet.* 16(5-6): 339-46 (1989).

For electroporation, freshly-grown yeast cultures are typically washed, suspended in an osmotic protectant, such as sorbitol, mixed with DNA, and the cell suspension
20 pulsed in an electroporation device. Subsequently, the cells are spread on the surface of plates containing selective media. Becker *et al.*, *Methods Enzymol.* 194: 182-187 (1991). The efficiency of transformation by electroporation can be increased over 100-fold by using PEG, single-stranded carrier DNA and cells that are in late log-phase of growth. Larger constructs, such as YACs, can be introduced by protoplast fusion.

25 Mammalian and insect cells can be directly infected by packaged viral vectors, or transfected by chemical or electrical means. For chemical transfection, DNA can be coprecipitated with CaPO_4 or introduced using liposomal and nonliposomal lipid-based agents. Commercial kits are available for CaPO_4 transfection (CalPhos™ Mammalian Transfection Kit, Clontech Laboratories, Palo Alto, CA, USA), and lipid-mediated
30 transfection can be practiced using commercial reagents, such as LIPOFECTAMINE™ 2000, LIPOFECTAMINE™ Reagent, CELLFECTIN® Reagent, and LIPOFECTIN® Reagent (Invitrogen, Carlsbad, CA, USA), DOTAP Liposomal Transfection Reagent,

FuGENE 6, X-tremeGENE Q2, DOSPER, (Roche Molecular Biochemicals, Indianapolis, IN USA), Effectene™, PolyFect®, Superfect® (Qiagen, Inc., Valencia, CA, USA).

Protocols for electroporating mammalian cells can be found online in Electroprotocols (Bio-Rad, Richmond, CA, USA) (<http://www.bio-rad.com/LifeScience/pdf/>

- 5 New_Gene_Pulser.pdf); Norton *et al.* (eds.), Gene Transfer Methods: Introducing DNA into Living Cells and Organisms, BioTechniques Books, Eaton Publishing Co. (2000); incorporated herein by reference in its entirety. Other transfection techniques include transfection by particle bombardment and microinjection. *See, e.g.,* Cheng *et al.*, *Proc. Natl. Acad. Sci. USA* 90(10): 4455-9 (1993); Yang *et al.*, *Proc. Natl. Acad. Sci. USA*
10 87(24): 9568-72 (1990).

Production of the recombinantly produced proteins of the present invention can optionally be followed by purification.

- Purification of recombinantly expressed proteins is now well by those skilled in the art. *See, e.g.,* Thorner *et al.* (eds.), Applications of Chimeric Genes and Hybrid
15 Proteins, Part A: Gene Expression and Protein Purification (Methods in Enzymology, Vol. 326), Academic Press (2000); Harbin (ed.), Cloning, Gene Expression and Protein Purification : Experimental Procedures and Process Rationale, Oxford Univ. Press (2001); Marshak *et al.*, Strategies for Protein Purification and Characterization: A Laboratory Course Manual, Cold Spring Harbor Laboratory Press (1996); and Roe (ed.),
20 Protein Purification Applications, Oxford University Press (2001); the disclosures of which are incorporated herein by reference in their entireties, and thus need not be detailed here.

- Briefly, however, if purification tags have been fused through use of an expression vector that appends such tags, purification can be effected, at least in part, by
25 means appropriate to the tag, such as use of immobilized metal affinity chromatography for polyhistidine tags. Other techniques common in the art include ammonium sulfate fractionation, immunoprecipitation, fast protein liquid chromatography (FPLC), high performance liquid chromatography (HPLC), and preparative gel electrophoresis.

Polypeptides

- 30 Another object of the invention is to provide polypeptides encoded by the nucleic acid molecules of the instant invention. In a preferred embodiment, the polypeptide is a breast specific polypeptide (BSP). In an even more preferred embodiment, the

polypeptide is derived from a polypeptide comprising the amino acid sequence of SEQ ID NO: 165 through 280. A polypeptide as defined herein may be produced recombinantly, as discussed *supra*, may be isolated from a cell that naturally expresses the protein, or may be chemically synthesized following the teachings of the specification and using methods well-known to those having ordinary skill in the art.

In another aspect, the polypeptide may comprise a fragment of a polypeptide, wherein the fragment is as defined herein. In a preferred embodiment, the polypeptide fragment is a fragment of a BSP. In a more preferred embodiment, the fragment is derived from a polypeptide comprising the amino acid sequence of SEQ ID NO: 165 through 280. A polypeptide that comprises only a fragment of an entire BSP may or may not be a polypeptide that is also a BSP. For instance, a full-length polypeptide may be breast-specific, while a fragment thereof may be found in other tissues as well as in breast. A polypeptide that is not a BSP, whether it is a fragment, analog, mutein, homologous protein or derivative, is nevertheless useful, especially for immunizing animals to prepare anti-BSP antibodies. However, in a preferred embodiment, the part or fragment is a BSP. Methods of determining whether a polypeptide is a BSP are described *infra*.

Fragments of at least 6 contiguous amino acids are useful in mapping B cell and T cell epitopes of the reference protein. *See, e.g., Geysen et al., Proc. Natl. Acad. Sci. USA* 81: 3998-4002 (1984) and U.S. Patents 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. Because the fragment need not itself be immunogenic, part of an immunodominant epitope, nor even recognized by native antibody, to be useful in such epitope mapping, all fragments of at least 6 amino acids of the proteins of the present invention have utility in such a study.

Fragments of at least 8 contiguous amino acids, often at least 15 contiguous amino acids, are useful as immunogens for raising antibodies that recognize the proteins of the present invention. *See, e.g., Lerner, Nature* 299: 592-596 (1982); Shinnick *et al., Annu. Rev. Microbiol.* 37: 425-46 (1983); Sutcliffe *et al., Science* 219: 660-6 (1983), the disclosures of which are incorporated herein by reference in their entireties. As further described in the above-cited references, virtually all 8-mers, conjugated to a carrier, such as a protein, prove immunogenic, meaning that they are capable of eliciting antibody for

the conjugated peptide; accordingly, all fragments of at least 8 amino acids of the proteins of the present invention have utility as immunogens.

Fragments of at least 8, 9, 10 or 12 contiguous amino acids are also useful as competitive inhibitors of binding of the entire protein, or a portion thereof, to antibodies (as in epitope mapping), and to natural binding partners, such as subunits in a multimeric complex or to receptors or ligands of the subject protein; this competitive inhibition permits identification and separation of molecules that bind specifically to the protein of interest, U.S. Patents 5,539,084 and 5,783,674, incorporated herein by reference in their entireties.

10 The protein, or protein fragment, of the present invention is thus at least 6 amino acids in length, typically at least 8, 9, 10 or 12 amino acids in length, and often at least 15 amino acids in length. Often, the protein of the present invention, or fragment thereof, is at least 20 amino acids in length, even 25 amino acids, 30 amino acids, 35 amino acids, or 50 amino acids or more in length. Of course, larger fragments having at least 75
15 amino acids, 100 amino acids, or even 150 amino acids are also useful, and at times preferred.

One having ordinary skill in the art can produce fragments of a polypeptide by truncating the nucleic acid molecule, *e.g.*, a BSNA, encoding the polypeptide and then expressing it recombinantly. Alternatively, one can produce a fragment by chemically
20 synthesizing a portion of the full-length polypeptide. One may also produce a fragment by enzymatically cleaving either a recombinant polypeptide or an isolated naturally-occurring polypeptide. Methods of producing polypeptide fragments are well-known in the art. *See, e.g.*, Sambrook (1989), *supra*; Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. In one embodiment, a polypeptide comprising only a
25 fragment of polypeptide of the invention, preferably a BSP, may be produced by chemical or enzymatic cleavage of a polypeptide. In a preferred embodiment, a polypeptide fragment is produced by expressing a nucleic acid molecule encoding a fragment of the polypeptide, preferably a BSP, in a host cell.

By "polypeptides" as used herein it is also meant to be inclusive of mutants,
30 fusion proteins, homologous proteins and allelic variants of the polypeptides specifically exemplified.

A mutant protein, or mutein, may have the same or different properties compared to a naturally-occurring polypeptide and comprises at least one amino acid insertion, duplication, deletion, rearrangement or substitution compared to the amino acid sequence of a native protein. Small deletions and insertions can often be found that do not alter the function of the protein. In one embodiment, the mutein may or may not be breast-specific. In a preferred embodiment, the mutein is breast-specific. In a preferred embodiment, the mutein is a polypeptide that comprises at least one amino acid insertion, duplication, deletion, rearrangement or substitution compared to the amino acid sequence of SEQ ID NO: 164 through 280. In a more preferred embodiment, the mutein is one that exhibits at least 50% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more preferably at least 80% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 165 through 280. In yet a more preferred embodiment, the mutein exhibits at least 85%, more preferably 90%, even more preferably 95% or 96%, and yet more preferably at least 97%, 98%, 99% or 99.5% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 165 through 280.

A mutein may be produced by isolation from a naturally-occurring mutant cell, tissue or organism. A mutein may be produced by isolation from a cell, tissue or organism that has been experimentally mutagenized. Alternatively, a mutein may be produced by chemical manipulation of a polypeptide, such as by altering the amino acid residue to another amino acid residue using synthetic or semi-synthetic chemical techniques. In a preferred embodiment, a mutein may be produced from a host cell comprising an altered nucleic acid molecule compared to the naturally-occurring nucleic acid molecule. For instance, one may produce a mutein of a polypeptide by introducing one or more mutations into a nucleic acid sequence of the invention and then expressing it recombinantly. These mutations may be targeted, in which particular encoded amino acids are altered, or may be untargeted, in which random encoded amino acids within the polypeptide are altered. Muteins with random amino acid alterations can be screened for a particular biological activity or property, particularly whether the polypeptide is breast-specific, as described below. Multiple random mutations can be introduced into the gene by methods well-known to the art, *e.g.*, by error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, *in vivo*

mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis and site-specific mutagenesis. Methods of producing muteins with targeted or random amino acid alterations are well-known in the art. *See, e.g.,* Sambrook (1989), *supra*; Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel
5 (1999), U.S. Patent 5,223,408, and the references discussed *supra*, each herein incorporated by reference.

By "polypeptide" as used herein it is also meant to be inclusive of polypeptides homologous to those polypeptides exemplified herein. In a preferred embodiment, the polypeptide is homologous to a BSP. In an even more preferred embodiment, the
10 polypeptide is homologous to a BSP selected from the group having an amino acid sequence of SEQ ID NO: 165 through 280. In a preferred embodiment, the homologous polypeptide is one that exhibits significant sequence identity to a BSP. In a more preferred embodiment, the polypeptide is one that exhibits significant sequence identity to an comprising an amino acid sequence of SEQ ID NO: 165 through 280. In an even
15 more preferred embodiment, the homologous polypeptide is one that exhibits at least 50% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more preferably at least 80% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 165 through 280. In a yet more preferred embodiment, the homologous polypeptide is one that exhibits at least 85%,
20 more preferably 90%, even more preferably 95% or 96%, and yet more preferably at least 97% or 98% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 165 through 280. In another preferred embodiment, the homologous polypeptide is one that exhibits at least 99%, more preferably 99.5%, even more preferably 99.6%, 99.7%, 99.8% or 99.9% sequence identity to a BSP comprising an amino acid sequence
25 of SEQ ID NO: 165 through 280. In a preferred embodiment, the amino acid substitutions are conservative amino acid substitutions as discussed above.

In another embodiment, the homologous polypeptide is one that is encoded by a nucleic acid molecule that selectively hybridizes to a BSNA. In a preferred embodiment, the homologous polypeptide is encoded by a nucleic acid molecule that hybridizes to a
30 BSNA under low stringency, moderate stringency or high stringency conditions, as defined herein. In a more preferred embodiment, the BSNA is selected from the group consisting of SEQ ID NO: 1 through 164. In another preferred embodiment, the

homologous polypeptide is encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule that encodes a BSP under low stringency, moderate stringency or high stringency conditions, as defined herein. In a more preferred embodiment, the BSP is selected from the group consisting of SEQ ID NO: 165 through 280.

- 5 The homologous polypeptide may be a naturally-occurring one that is derived from another species, especially one derived from another primate, such as chimpanzee, gorilla, rhesus macaque, baboon or gorilla, wherein the homologous polypeptide comprises an amino acid sequence that exhibits significant sequence identity to that of SEQ ID NO: 165 through 280. The homologous polypeptide may also be a naturally-
10 occurring polypeptide from a human, when the BSP is a member of a family of polypeptides. The homologous polypeptide may also be a naturally-occurring polypeptide derived from a non-primate, mammalian species, including without limitation, domesticated species, *e.g.*, dog, cat, mouse, rat, rabbit, guinea pig, hamster, cow, horse, goat or pig. The homologous polypeptide may also be a naturally-occurring
15 polypeptide derived from a non-mammalian species, such as birds or reptiles. The naturally-occurring homologous protein may be isolated directly from humans or other species. Alternatively, the nucleic acid molecule encoding the naturally-occurring homologous polypeptide may be isolated and used to express the homologous polypeptide recombinantly. In another embodiment, the homologous polypeptide may be
20 one that is experimentally produced by random mutation of a nucleic acid molecule and subsequent expression of the nucleic acid molecule. In another embodiment, the homologous polypeptide may be one that is experimentally produced by directed mutation of one or more codons to alter the encoded amino acid of a BSP. Further, the homologous protein may or may not encode polypeptide that is a BSP. However, in a
25 preferred embodiment, the homologous polypeptide encodes a polypeptide that is a BSP.

- Relatedness of proteins can also be characterized using a second functional test, the ability of a first protein competitively to inhibit the binding of a second protein to an antibody. It is, therefore, another aspect of the present invention to provide isolated proteins not only identical in sequence to those described with particularity herein, but
30 also to provide isolated proteins ("cross-reactive proteins") that competitively inhibit the binding of antibodies to all or to a portion of various of the isolated polypeptides of the

present invention. Such competitive inhibition can readily be determined using immunoassays well-known in the art.

As discussed above, single nucleotide polymorphisms (SNPs) occur frequently in eukaryotic genomes, and the sequence determined from one individual of a species may differ from other allelic forms present within the population. Thus, by "polypeptide" as used herein it is also meant to be inclusive of polypeptides encoded by an allelic variant of a nucleic acid molecule encoding a BSP. In a preferred embodiment, the polypeptide is encoded by an allelic variant of a gene that encodes a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO: 165 through 280. In a yet more preferred embodiment, the polypeptide is encoded by an allelic variant of a gene that has the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1 through 164.

In another embodiment, the invention provides polypeptides which comprise derivatives of a polypeptide encoded by a nucleic acid molecule according to the instant invention. In a preferred embodiment, the polypeptide is a BSP. In a preferred embodiment, the polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO: 165 through 280, or is a mutein, allelic variant, homologous protein or fragment thereof. In a preferred embodiment, the derivative has been acetylated, carboxylated, phosphorylated, glycosylated or ubiquitinated. In another preferred embodiment, the derivative has been labeled with, *e.g.*, radioactive isotopes such as ^{125}I , ^{32}P , ^{35}S , and ^3H . In another preferred embodiment, the derivative has been labeled with fluorophores, chemiluminescent agents, enzymes, and antiligands that can serve as specific binding pair members for a labeled ligand.

Polypeptide modifications are well-known to those of skill and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as, for instance Creighton, Protein Structure and Molecular Properties, 2nd ed., W. H. Freeman and Company (1993). Many detailed reviews are available on this subject, such as, for example, those provided by Wold, in Johnson (ed.), Posttranslational Covalent Modification of Proteins, pgs. 1-12, Academic Press (1983);

Seifter *et al.*, *Meth. Enzymol.* 182: 626-646 (1990) and Rattan *et al.*, *Ann. N.Y. Acad. Sci.* 663: 48-62 (1992).

It will be appreciated, as is well-known and as noted above, that polypeptides are not always entirely linear. For instance, polypeptides may be branched as a result of ubiquitination, and they may be circular, with or without branching, generally as a result of posttranslation events, including natural processing event and events brought about by human manipulation which do not occur naturally. Circular, branched and branched circular polypeptides may be synthesized by non-translation natural process and by entirely synthetic methods, as well. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. In fact, blockage of the amino or carboxyl group in a polypeptide, or both, by a covalent modification, is common in naturally occurring and synthetic polypeptides and such modifications may be present in polypeptides of the present invention, as well. For instance, the amino terminal residue of polypeptides made in *E. coli*, prior to proteolytic processing, almost invariably will be N-formylmethionine.

Useful post-synthetic (and post-translational) modifications include conjugation to detectable labels, such as fluorophores. A wide variety of amine-reactive and thiol-reactive fluorophore derivatives have been synthesized that react under nondenaturing conditions with N-terminal amino groups and epsilon amino groups of lysine residues, on the one hand, and with free thiol groups of cysteine residues, on the other.

Kits are available commercially that permit conjugation of proteins to a variety of amine-reactive or thiol-reactive fluorophores: Molecular Probes, Inc. (Eugene, OR, USA), *e.g.*, offers kits for conjugating proteins to Alexa Fluor 350, Alexa Fluor 430, Fluorescein-EX, Alexa Fluor 488, Oregon Green 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, and Texas Red-X.

A wide variety of other amine-reactive and thiol-reactive fluorophores are available commercially (Molecular Probes, Inc., Eugene, OR, USA), including Alexa Fluor® 350, Alexa Fluor® 488, Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc., Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591,

BODIPY TR, BODIPY 630/650, BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B, Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from Molecular Probes, Inc., Eugene, OR, USA).

- 5 The polypeptides of the present invention can also be conjugated to fluorophores, other proteins, and other macromolecules, using bifunctional linking reagents. Common homobifunctional reagents include, *e.g.*, APG, AEDP, BASED, BMB, BMDB, BMH, BMOE, BM[PEO]3, BM[PEO]4, BS3, BSOE, DFDNB, DMA, DMP, DMS, DPDPB, DSG, DSP (Lomant's Reagent), DSS, DST, DTBP, DTME, DTSSP, EGS, HBVS, Sulfo-BSOE, Sulfo-DST, Sulfo-EGS (all available from Pierce, Rockford, IL, USA); common heterobifunctional cross-linkers include ABH, AMAS, ANB-NOS, APDP, ASBA, BMFA, BMPH, BMPS, EDC, EMCA, EMCH, EMCS, KMUA, KMH, GMBS, LC-SMCC, LC-SPDP, MBS, M2C2H, MPBH, MSA, NHS-ASA, PDPH, PMPI, SADP, SAED, SAND, SANPAH, SASD, SATP, SBAP, SFAD, SIA, SIAB, SMCC, SMPB, SMPH, SMPT, SPDP, Sulfo-EMCS, Sulfo-GMBS, Sulfo-HSAB, Sulfo-KMH, Sulfo-LC-SPDP, Sulfo-MBS, Sulfo-NHS-LC-ASA, Sulfo-SADP, Sulfo-SANPAH, Sulfo-SIAB, Sulfo-SMCC, Sulfo-SMPB, Sulfo-LC-SMPT, SVSB, TFCS (all available
- 10
- 15
- Pierce, Rockford, IL, USA).

- The polypeptides, fragments, and fusion proteins of the present invention can be
- 20 conjugated, using such cross-linking reagents, to fluorophores that are not amine- or thiol-reactive. Other labels that usefully can be conjugated to the polypeptides, fragments, and fusion proteins of the present invention include radioactive labels, echosonographic contrast reagents, and MRI contrast agents.

- The polypeptides, fragments, and fusion proteins of the present invention can also
- 25 usefully be conjugated using cross-linking agents to carrier proteins, such as KLH, bovine thyroglobulin, and even bovine serum albumin (BSA), to increase immunogenicity for raising anti-BSP antibodies.

- The polypeptides, fragments, and fusion proteins of the present invention can also
- 30 usefully be conjugated to polyethylene glycol (PEG); PEGylation increases the serum half-life of proteins administered intravenously for replacement therapy. Delgado *et al.*, *Crit. Rev. Ther. Drug Carrier Syst.* 9(3-4): 249-304 (1992); Scott *et al.*, *Curr. Pharm. Des.* 4(6): 423-38 (1998); DeSantis *et al.*, *Curr. Opin. Biotechnol.* 10(4): 324-30 (1999),

incorporated herein by reference in their entireties. PEG monomers can be attached to the protein directly or through a linker, with PEGylation using PEG monomers activated with tresyl chloride (2,2,2-trifluoroethanesulphonyl chloride) permitting direct attachment under mild conditions.

- 5 In yet another embodiment, the invention provides analogs of a polypeptide encoded by a nucleic acid molecule according to the instant invention. In a preferred embodiment, the polypeptide is a BSP. In a more preferred embodiment, the analog is derived from a polypeptide having part or all of the amino acid sequence of SEQ ID NO: 165 through 280. In a preferred embodiment, the analog is one that comprises one or
- 10 more substitutions of non-natural amino acids or non-native inter-residue bonds compared to the naturally-occurring polypeptide. In general, the non-peptide analog is structurally similar to a BSP, but one or more peptide linkages is replaced by a linkage selected from the group consisting of --CH₂NH--, --CH₂S--, --CH₂-CH₂--,
- 15 --CH=CH--(cis and trans), --COCH₂--, --CH(OH)CH₂-- and --CH₂SO--. In another embodiment, the non-peptide analog comprises substitution of one or more amino acids of a BSP with a D-amino acid of the same type or other non-natural amino acid in order to generate more stable peptides. D-amino acids can readily be incorporated during chemical peptide synthesis: peptides assembled from D-amino acids are more resistant to proteolytic attack; incorporation of D-amino acids can also be used to confer specific
- 20 three-dimensional conformations on the peptide. Other amino acid analogues commonly added during chemical synthesis include ornithine, norleucine, phosphorylated amino acids (typically phosphoserine, phosphothreonine, phosphotyrosine), L-malonyltyrosine, a non-hydrolyzable analog of phosphotyrosine (*see, e.g., Krole et al., Biochem. Biophys. Res. Com.* 209: 817-821 (1995)), and various halogenated phenylalanine derivatives.
- 25 Non-natural amino acids can be incorporated during solid phase chemical synthesis or by recombinant techniques, although the former is typically more common. Solid phase chemical synthesis of peptides is well established in the art. Procedures are described, inter alia, in Chan *et al.* (eds.), Fmoc Solid Phase Peptide Synthesis: A Practical Approach (Practical Approach Series), Oxford Univ. Press (March 2000);
- 30 Jones, Amino Acid and Peptide Synthesis (Oxford Chemistry Primers, No 7), Oxford Univ. Press (1992); and Bodanszky, Principles of Peptide Synthesis (Springer

Laboratory), Springer Verlag (1993); the disclosures of which are incorporated herein by reference in their entirety.

Amino acid analogues having detectable labels are also usefully incorporated during synthesis to provide derivatives and analogs. Biotin, for example can be added
5 using biotinoyl-(9-fluorenylmethoxycarbonyl)-L-lysine (Fmoc biocytin) (Molecular Probes, Eugene, OR, USA). Biotin can also be added enzymatically by incorporation into a fusion protein of a *E. coli* BirA substrate peptide. The Fmoc and *t*BOC derivatives of dabcyL-L-lysine (Molecular Probes, Inc., Eugene, OR, USA) can be used to incorporate the dabcyL chromophore at selected sites in the peptide sequence during
10 synthesis. The aminonaphthalene derivative EDANS, the most common fluorophore for pairing with the dabcyL quencher in fluorescence resonance energy transfer (FRET) systems, can be introduced during automated synthesis of peptides by using EDANS-Fmoc-L-glutamic acid or the corresponding *t*BOC derivative (both from Molecular Probes, Inc., Eugene, OR, USA). Tetramethylrhodamine fluorophores can be
15 incorporated during automated Fmoc synthesis of peptides using (Fmoc)-TMR-L-lysine (Molecular Probes, Inc. Eugene, OR, USA).

Other useful amino acid analogues that can be incorporated during chemical synthesis include aspartic acid, glutamic acid, lysine, and tyrosine analogues having allyl side-chain protection (Applied Biosystems, Inc., Foster City, CA, USA); the allyl side
20 chain permits synthesis of cyclic, branched-chain, sulfonated, glycosylated, and phosphorylated peptides.

A large number of other Fmoc-protected non-natural amino acid analogues capable of incorporation during chemical synthesis are available commercially, including, *e.g.*, Fmoc-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid, Fmoc-3-endo-
25 aminobicyclo[2.2.1]heptane-2-endo-carboxylic acid, Fmoc-3-exo-aminobicyclo[2.2.1]heptane-2-exo-carboxylic acid, Fmoc-3-endo-amino-bicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid, Fmoc-3-exo-amino-bicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acid, Fmoc-cis-2-amino-1-cyclohexanecarboxylic acid, Fmoc-trans-2-amino-1-cyclohexanecarboxylic acid, Fmoc-1-amino-1-cyclopentanecarboxylic
30 acid, Fmoc-cis-2-amino-1-cyclopentanecarboxylic acid, Fmoc-1-amino-1-cyclopropanecarboxylic acid, Fmoc-D-2-amino-4-(ethylthio)butyric acid, Fmoc-L-2-amino-4-(ethylthio)butyric acid, Fmoc-L-buthionine, Fmoc-S-methyl-L-Cysteine, Fmoc-

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2-aminobenzoic acid (anthranillic acid), Fmoc-3-aminobenzoic acid, Fmoc-4-aminobenzoic acid, Fmoc-2-aminobenzophenone-2'-carboxylic acid, Fmoc-N-(4-aminobenzoyl)- β -alanine, Fmoc-2-amino-4,5-dimethoxybenzoic acid, Fmoc-4-aminohippuric acid, Fmoc-2-amino-3-hydroxybenzoic acid, Fmoc-2-amino-5-hydroxybenzoic acid, Fmoc-3-amino-4-hydroxybenzoic acid, Fmoc-4-amino-3-hydroxybenzoic acid, Fmoc-4-amino-2-hydroxybenzoic acid, Fmoc-5-amino-2-hydroxybenzoic acid, Fmoc-2-amino-3-methoxybenzoic acid, Fmoc-4-amino-3-methoxybenzoic acid, Fmoc-2-amino-3-methylbenzoic acid, Fmoc-2-amino-5-methylbenzoic acid, Fmoc-2-amino-6-methylbenzoic acid, Fmoc-3-amino-2-methylbenzoic acid, Fmoc-3-amino-4-methylbenzoic acid, Fmoc-4-amino-3-methylbenzoic acid, Fmoc-3-amino-2-naphtoic acid, Fmoc-D,L-3-amino-3-phenylpropionic acid, Fmoc-L-Methyldopa, Fmoc-2-amino-4,6-dimethyl-3-pyridinecarboxylic acid, Fmoc-D,L-amino-2-thiophenacetic acid, Fmoc-4-(carboxymethyl)piperazine, Fmoc-4-carboxypiperazine, Fmoc-4-(carboxymethyl)homopiperazine, Fmoc-4-phenyl-4-piperidinecarboxylic acid, Fmoc-L-1,2,3,4-tetrahydronorharman-3-carboxylic acid, Fmoc-L-thiazolidine-4-carboxylic acid, all available from The Peptide Laboratory (Richmond, CA, USA).

Non-natural residues can also be added biosynthetically by engineering a suppressor tRNA, typically one that recognizes the UAG stop codon, by chemical aminoacylation with the desired unnatural amino acid. Conventional site-directed mutagenesis is used to introduce the chosen stop codon UAG at the site of interest in the protein gene. When the acylated suppressor tRNA and the mutant gene are combined in an *in vitro* transcription/translation system, the unnatural amino acid is incorporated in response to the UAG codon to give a protein containing that amino acid at the specified position. Liu *et al.*, *Proc. Natl Acad. Sci. USA* 96(9): 4780-5 (1999); Wang *et al.*, *Science* 292(5516): 498-500 (2001).

Fusion Proteins

The present invention further provides fusions of each of the polypeptides and fragments of the present invention to heterologous polypeptides. In a preferred embodiment, the polypeptide is a BSP. In a more preferred embodiment, the polypeptide that is fused to the heterologous polypeptide comprises part or all of the amino acid sequence of SEQ ID NO: 165 through 280, or is a mutein, homologous polypeptide,

analog or derivative thereof. In an even more preferred embodiment, the nucleic acid molecule encoding the fusion protein comprises all or part of the nucleic acid sequence of SEQ ID NO: 1 through 164, or comprises all or part of a nucleic acid sequence that selectively hybridizes or is homologous to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1 through 164.

The fusion proteins of the present invention will include at least one fragment of the protein of the present invention, which fragment is at least 6, typically at least 8, often at least 15, and usefully at least 16, 17, 18, 19, or 20 amino acids long. The fragment of the protein of the present to be included in the fusion can usefully be at least 25 amino acids long, at least 50 amino acids long, and can be at least 75, 100, or even 150 amino acids long. Fusions that include the entirety of the proteins of the present invention have particular utility.

The heterologous polypeptide included within the fusion protein of the present invention is at least 6 amino acids in length, often at least 8 amino acids in length, and usefully at least 15, 20, and 25 amino acids in length. Fusions that include larger polypeptides, such as the IgG Fc region, and even entire proteins (such as GFP chromophore-containing proteins) are particularly useful.

As described above in the description of vectors and expression vectors of the present invention, which discussion is incorporated here by reference in its entirety, heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those designed to facilitate purification and/or visualization of recombinantly-expressed proteins. *See, e.g., Ausubel, Chapter 16, (1992), supra.* Although purification tags can also be incorporated into fusions that are chemically synthesized, chemical synthesis typically provides sufficient purity that further purification by HPLC suffices; however, visualization tags as above described retain their utility even when the protein is produced by chemical synthesis, and when so included render the fusion proteins of the present invention useful as directly detectable markers of the presence of a polypeptide of the invention.

As also discussed above, heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those that facilitate secretion of recombinantly expressed proteins — into the periplasmic space or extracellular milieu for prokaryotic hosts, into the culture medium for eukaryotic cells — through incorporation

of secretion signals and/or leader sequences. For example, a His⁶ tagged protein can be purified on a Ni affinity column and a GST fusion protein can be purified on a glutathione affinity column. Similarly, a fusion protein comprising the Fc domain of IgG can be purified on a Protein A or Protein G column and a fusion protein comprising an epitope tag such as myc can be purified using an immunoaffinity column containing an anti-c-myc antibody. It is preferable that the epitope tag be separated from the protein encoded by the essential gene by an enzymatic cleavage site that can be cleaved after purification. See also the discussion of nucleic acid molecules encoding fusion proteins that may be expressed on the surface of a cell.

- 10 Other useful protein fusions of the present invention include those that permit use of the protein of the present invention as bait in a yeast two-hybrid system. See Bartel *et al.* (eds.), The Yeast Two-Hybrid System, Oxford University Press (1997); Zhu *et al.*, Yeast Hybrid Technologies, Eaton Publishing (2000); Fields *et al.*, *Trends Genet.* 10(8): 286-92 (1994); Mendelsohn *et al.*, *Curr. Opin. Biotechnol.* 5(5): 482-6 (1994); Luban *et al.*, *Curr. Opin. Biotechnol.* 6(1): 59-64 (1995); Allen *et al.*, *Trends Biochem. Sci.* 20(12): 511-6 (1995); Drees, *Curr. Opin. Chem. Biol.* 3(1): 64-70 (1999); Topcu *et al.*, *Pharm. Res.* 17(9): 1049-55 (2000); Fashena *et al.*, *Gene* 250(1-2): 1-14 (2000); ; Colas *et al.*, (1996) Genetic selection of peptide aptamers that recognize and inhibit cyclin-dependent kinase 2. *Nature* 380, 548-550; Norman, T. *et al.*, (1999) Genetic selection of peptide inhibitors of biological pathways. *Science* 285, 591-595, Fabbri *et al.*, (1999) Inhibition of mammalian cell proliferation by genetically selected peptide aptamers that functionally antagonize E2F activity. *Oncogene* 18, 4357-4363; Xu *et al.*, (1997) Cells that register logical relationships among proteins. *Proc Natl Acad Sci U S A.* 94, 12473-12478; Yang, *et al.*, (1995) Protein-peptide interactions analyzed with the yeast two-
25 hybrid system. *Nuc. Acids Res.* 23, 1152-1156; Kolonin *et al.*, (1998) Targeting cyclin-dependent kinases in Drosophila with peptide aptamers. *Proc Natl Acad Sci U S A* 95, 14266-14271; Cohen *et al.*, (1998) An artificial cell-cycle inhibitor isolated from a combinatorial library. *Proc Natl Acad Sci U S A* 95, 14272-14277; Uetz, P.; Giot, L.; al, e.; Fields, S.; Rothberg, J. M. (2000) A comprehensive analysis of protein-protein
30 interactions in *Saccharomyces cerevisiae*. *Nature* 403, 623-627; Ito, *et al.*, (2001) A comprehensive two-hybrid analysis to explore the yeast protein interactome. *Proc Natl Acad Sci U S A* 98, 4569-4574, the disclosures of which are incorporated herein by

reference in their entirety. Typically, such fusion is to either *E. coli* LexA or yeast GAL4 DNA binding domains. Related bait plasmids are available that express the bait fused to a nuclear localization signal.

Other useful fusion proteins include those that permit display of the encoded
5 protein on the surface of a phage or cell, fusions to intrinsically fluorescent proteins, such as green fluorescent protein (GFP), and fusions to the IgG Fc region, as described above, which discussion is incorporated here by reference in its entirety.

The polypeptides and fragments of the present invention can also usefully be fused to protein toxins, such as *Pseudomonas* exotoxin A, *diphtheria* toxin, *shiga* toxin
10 A, *anthrax* toxin lethal factor, ricin, in order to effect ablation of cells that bind or take up the proteins of the present invention.

Fusion partners include, *inter alia*, *myc*, hemagglutinin (HA), GST, immunoglobulins, β -galactosidase, biotin trpE, protein A, β -lactamase, α -amylase, maltose binding protein, alcohol dehydrogenase, polyhistidine (for example, six histidine
15 at the amino and/or carboxyl terminus of the polypeptide), lacZ, green fluorescent protein (GFP), yeast ϕ -mating factor, GAL4 transcription activation or DNA binding domain, luciferase, and serum proteins such as ovalbumin, albumin and the constant domain of IgG. *See, e.g.*, Ausubel (1992), *supra* and Ausubel (1999), *supra*. Fusion proteins may also contain sites for specific enzymatic cleavage, such as a site that is recognized by
20 enzymes such as Factor XIII, trypsin, pepsin, or any other enzyme known in the art. Fusion proteins will typically be made by either recombinant nucleic acid methods, as described above, chemically synthesized using techniques well-known in the art (*e.g.*, a Merrifield synthesis), or produced by chemical cross-linking.

Another advantage of fusion proteins is that the epitope tag can be used to bind
25 the fusion protein to a plate or column through an affinity linkage for screening binding proteins or other molecules that bind to the BSP.

As further described below, the isolated polypeptides, muteins, fusion proteins, homologous proteins or allelic variants of the present invention can readily be used as specific immunogens to raise antibodies that specifically recognize BSPs, their allelic
30 variants and homologues. The antibodies, in turn, can be used, *inter alia*, specifically to assay for the polypeptides of the present invention, particularly BSPs, *e.g.* by ELISA for detection of protein fluid samples, such as serum, by immunohistochemistry or laser

scanning cytometry, for detection of protein in tissue samples, or by flow cytometry, for detection of intracellular protein in cell suspensions, for specific antibody-mediated isolation and/or purification of BSPs, as for example by immunoprecipitation, and for use as specific agonists or antagonists of BSPs.

- 5 One may determine whether polypeptides including muteins, fusion proteins, homologous proteins or allelic variants are functional by methods known in the art. For instance, residues that are tolerant of change while retaining function can be identified by altering the protein at known residues using methods known in the art, such as alanine scanning mutagenesis, Cunningham *et al.*, *Science* 244(4908): 1081-5 (1989); transposon linker scanning mutagenesis, Chen *et al.*, *Gene* 263(1-2): 39-48 (2001); combinations of homolog- and alanine-scanning mutagenesis, Jin *et al.*, *J. Mol. Biol.* 226(3): 851-65 (1992); combinatorial alanine scanning, Weiss *et al.*, *Proc. Natl. Acad. Sci USA* 97(16): 8950-4 (2000), followed by functional assay. Transposon linker scanning kits are available commercially (New England Biolabs, Beverly, MA, USA, catalog. no. E7-102S; EZ::TN™ In-Frame Linker Insertion Kit, catalogue no. EZI04KN, Epicentre Technologies Corporation, Madison, WI, USA).

Purification of the polypeptides including fragments, homologous polypeptides, muteins, analogs, derivatives and fusion proteins is well-known and within the skill of one having ordinary skill in the art. See, *e.g.*, Scopes, Protein Purification, 2d ed. (1987).

- 20 Purification of recombinantly expressed polypeptides is described above. Purification of chemically-synthesized peptides can readily be effected, *e.g.*, by HPLC.

- Accordingly, it is an aspect of the present invention to provide the isolated proteins of the present invention in pure or substantially pure form in the presence of absence of a stabilizing agent. Stabilizing agents include both proteinaceous or non-proteinaceous material and are well-known in the art. Stabilizing agents, such as albumin and polyethylene glycol (PEG) are known and are commercially available.

- Although high levels of purity are preferred when the isolated proteins of the present invention are used as therapeutic agents, such as in vaccines and as replacement therapy, the isolated proteins of the present invention are also useful at lower purity. For example, partially purified proteins of the present invention can be used as immunogens to raise antibodies in laboratory animals.

In preferred embodiments, the purified and substantially purified proteins of the present invention are in compositions that lack detectable ampholytes, acrylamide monomers, bis-acrylamide monomers, and polyacrylamide.

The polypeptides, fragments, analogs, derivatives and fusions of the present invention can usefully be attached to a substrate. The substrate can be porous or solid, planar or non-planar; the bond can be covalent or noncovalent.

For example, the polypeptides, fragments, analogs, derivatives and fusions of the present invention can usefully be bound to a porous substrate, commonly a membrane, typically comprising nitrocellulose, polyvinylidene fluoride (PVDF), or cationically derivatized, hydrophilic PVDF; so bound, the proteins, fragments, and fusions of the present invention can be used to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized protein of the present invention.

As another example, the polypeptides, fragments, analogs, derivatives and fusions of the present invention can usefully be bound to a substantially nonporous substrate, such as plastic, to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized protein of the present invention. Such plastics include polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, polystyrene, polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, nitrocellulose, or mixtures thereof; when the assay is performed in a standard microtiter dish, the plastic is typically polystyrene.

The polypeptides, fragments, analogs, derivatives and fusions of the present invention can also be attached to a substrate suitable for use as a surface enhanced laser desorption ionization source; so attached, the protein, fragment, or fusion of the present invention is useful for binding and then detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound protein to indicate biologic interaction there between. The proteins, fragments, and fusions of the present invention can also be attached to a substrate suitable for use in surface plasmon resonance detection; so attached, the protein, fragment, or fusion of the present invention is useful for binding and then detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound protein to indicate biological interaction there between.

Antibodies

In another aspect, the invention provides antibodies, including fragments and derivatives thereof, that bind specifically to polypeptides encoded by the nucleic acid molecules of the invention, as well as antibodies that bind to fragments, muteins, derivatives and analogs of the polypeptides. In a preferred embodiment, the antibodies are specific for a polypeptide that is a BSP, or a fragment, mutein, derivative, analog or fusion protein thereof. In a more preferred embodiment, the antibodies are specific for a polypeptide that comprises SEQ ID NO: 165 through 280, or a fragment, mutein, derivative, analog or fusion protein thereof.

The antibodies of the present invention can be specific for linear epitopes, discontinuous epitopes, or conformational epitopes of such proteins or protein fragments, either as present on the protein in its native conformation or, in some cases, as present on the proteins as denatured, as, *e.g.*, by solubilization in SDS. New epitopes may be also due to a difference in post translational modifications (PTMs) in disease versus normal tissue. For example, a particular site on a BSP may be glycosylated in cancerous cells, but not glycosylated in normal cells or visa versa. In addition, alternative splice forms of a BSP may be indicative of cancer. Differential degradation of the C or N-terminus of a BSP may also be a marker or target for anticancer therapy. For example, a BSP may be N-terminal degraded in cancer cells exposing new epitopes to which antibodies may selectively bind for diagnostic or therapeutic uses.

As is well-known in the art, the degree to which an antibody can discriminate as among molecular species in a mixture will depend, in part, upon the conformational relatedness of the species in the mixture; typically, the antibodies of the present invention will discriminate over adventitious binding to non-BSP polypeptides by at least 2-fold, more typically by at least 5-fold, typically by more than 10-fold, 25-fold, 50-fold, 75-fold, and often by more than 100-fold, and on occasion by more than 500-fold or 1000-fold. When used to detect the proteins or protein fragments of the present invention, the antibody of the present invention is sufficiently specific when it can be used to determine the presence of the protein of the present invention in samples derived from human breast.

Typically, the affinity or avidity of an antibody (or antibody multimer, as in the case of an IgM pentamer) of the present invention for a protein or protein fragment of the

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present invention will be at least about 1×10^{-6} molar (M), typically at least about 5×10^{-7} M, 1×10^{-7} M, with affinities and avidities of at least 1×10^{-8} M, 5×10^{-9} M, 1×10^{-10} M and up to 1×10^{-13} M proving especially useful.

The antibodies of the present invention can be naturally-occurring forms, such as
5 IgG, IgM, IgD, IgE, IgY, and IgA, from any avian, reptilian, or mammalian species.

Human antibodies can, but will infrequently, be drawn directly from human donors or human cells. In this case, antibodies to the proteins of the present invention will typically have resulted from fortuitous immunization, such as autoimmune immunization, with the protein or protein fragments of the present invention. Such
10 antibodies will typically, but will not invariably, be polyclonal. In addition, individual polyclonal antibodies may be isolated and cloned to generate monoclonals.

Human antibodies are more frequently obtained using transgenic animals that express human immunoglobulin genes, which transgenic animals can be affirmatively immunized with the protein immunogen of the present invention. Human Ig-transgenic
15 mice capable of producing human antibodies and methods of producing human antibodies therefrom upon specific immunization are described, *inter alia*, in U.S. Patents 6,162,963; 6,150,584; 6,114,598; 6,075,181; 5,939,598; 5,877,397; 5,874,299; 5,814,318; 5,789,650; 5,770,429; 5,661,016; 5,633,425; 5,625,126; 5,569,825; 5,545,807; 5,545,806, and 5,591,669, the disclosures of which are incorporated herein by
20 reference in their entireties. Such antibodies are typically monoclonal, and are typically produced using techniques developed for production of murine antibodies.

Human antibodies are particularly useful, and often preferred, when the antibodies of the present invention are to be administered to human beings as *in vivo* diagnostic or therapeutic agents, since recipient immune response to the administered
25 antibody will often be substantially less than that occasioned by administration of an antibody derived from another species, such as mouse.

IgG, IgM, IgD, IgE, IgY, and IgA antibodies of the present invention can also be obtained from other species, including mammals such as rodents (typically mouse, but also rat, guinea pig, and hamster) lagomorphs, typically rabbits, and also larger
30 mammals, such as sheep, goats, cows, and horses, and other egg laying birds or reptiles such as chickens or alligators. For example, avian antibodies may be generated using techniques described in WO 00/29444, published 25 May 2000, the contents of which are

hereby incorporated in their entirety. In such cases, as with the transgenic human-antibody-producing non-human mammals, fortuitous immunization is not required, and the non-human mammal is typically affirmatively immunized, according to standard immunization protocols, with the protein or protein fragment of the present invention.

5 As discussed above, virtually all fragments of 8 or more contiguous amino acids of the proteins of the present invention can be used effectively as immunogens when conjugated to a carrier, typically a protein such as bovine thyroglobulin, keyhole limpet hemocyanin, or bovine serum albumin, conveniently using a bifunctional linker such as those described elsewhere above, which discussion is incorporated by reference here.

10 Immunogenicity can also be conferred by fusion of the polypeptide and fragments of the present invention to other moieties. For example, peptides of the present invention can be produced by solid phase synthesis on a branched polylysine core matrix; these multiple antigenic peptides (MAPs) provide high purity, increased avidity, accurate chemical definition and improved safety in vaccine development. Tam *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 5409-5413 (1988); Posnett *et al.*, *J. Biol. Chem.* 263: 1719-1725
15 (1988).

Protocols for immunizing non-human mammals or avian species are well-established in the art. See Harlow *et al.* (eds.), Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory (1998); Coligan *et al.* (eds.), Current Protocols in Immunology, John Wiley & Sons, Inc. (2001); Zola, Monoclonal Antibodies: Preparation and Use of Monoclonal Antibodies and Engineered Antibody Derivatives (Basics: From Background to Bench), Springer Verlag (2000); Gross M, Speck *J.Dtsch. Tierarztl. Wochenschr.* 103: 417-422 (1996), the disclosures of which are incorporated herein by
20 reference. Immunization protocols often include multiple immunizations, either with or without adjuvants such as Freund's complete adjuvant and Freund's incomplete adjuvant,
25 and may include naked DNA immunization (Moss, *Semin. Immunol.* 2: 317-327 (1990)).

Antibodies from non-human mammals and avian species can be polyclonal or monoclonal, with polyclonal antibodies having certain advantages in immunohistochemical detection of the proteins of the present invention and monoclonal
30 antibodies having advantages in identifying and distinguishing particular epitopes of the proteins of the present invention. Antibodies from avian species may have particular

advantage in detection of the proteins of the present invention, in human serum or tissues (Viking et al., *Biosens. Bioelectron.* 13: 1257-1262 (1998).

Following immunization, the antibodies of the present invention can be produced using any art-accepted technique. Such techniques are well-known in the art, Coligan, *supra*; Zola, *supra*; Howard *et al.* (eds.), Basic Methods in Antibody Production and Characterization, CRC Press (2000); Harlow, *supra*; Davis (ed.), Monoclonal Antibody Protocols, Vol. 45, Humana Press (1995); Delves (ed.), Antibody Production: Essential Techniques, John Wiley & Son Ltd (1997); Kenney, Antibody Solution: An Antibody Methods Manual, Chapman & Hall (1997), incorporated herein by reference in their
entireties, and thus need not be detailed here.

Briefly, however, such techniques include, *inter alia*, production of monoclonal antibodies by hybridomas and expression of antibodies or fragments or derivatives thereof from host cells engineered to express immunoglobulin genes or fragments thereof. These two methods of production are not mutually exclusive: genes encoding antibodies specific for the proteins or protein fragments of the present invention can be cloned from hybridomas and thereafter expressed in other host cells. Nor need the two necessarily be performed together: *e.g.*, genes encoding antibodies specific for the proteins and protein fragments of the present invention can be cloned directly from B cells known to be specific for the desired protein, as further described in U.S Patent 5,627,052, the disclosure of which is incorporated herein by reference in its entirety, or from antibody-displaying phage.

Recombinant expression in host cells is particularly useful when fragments or derivatives of the antibodies of the present invention are desired.

Host cells for recombinant production of either whole antibodies, antibody fragments, or antibody derivatives can be prokaryotic or eukaryotic.

Prokaryotic hosts are particularly useful for producing phage displayed antibodies of the present invention.

The technology of phage-displayed antibodies, in which antibody variable region fragments are fused, for example, to the gene III protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13, is by now well-established. *See, e.g.*, Sidhu, *Curr. Opin. Biotechnol.* 11(6): 610-6 (2000); Griffiths *et al.*, *Curr. Opin. Biotechnol.* 9(1): 102-8 (1998); Hoogenboom *et al.*, *Immunotechnology*,

4(1): 1-20 (1998); Rader *et al.*, *Current Opinion in Biotechnology* 8: 503-508 (1997); Aujame *et al.*, *Human Antibodies* 8: 155-168 (1997); Hoogenboom, *Trends in Biotechnol.* 15: 62-70 (1997); de Kruif *et al.*, 17: 453-455 (1996); Barbas *et al.*, *Trends in Biotechnol.* 14: 230-234 (1996); Winter *et al.*, *Ann. Rev. Immunol.* 433-455 (1994).

- 5 Techniques and protocols required to generate, propagate, screen (pan), and use the antibody fragments from such libraries have recently been compiled. *See, e.g.*, Barbas (2001), *supra*; Kay, *supra*; Abelson, *supra*, the disclosures of which are incorporated herein by reference in their entireties.

- Typically, phage-displayed antibody fragments are scFv fragments or Fab
10 fragments; when desired, full length antibodies can be produced by cloning the variable regions from the displaying phage into a complete antibody and expressing the full length antibody in a further prokaryotic or a eukaryotic host cell.

Eukaryotic cells are also useful for expression of the antibodies, antibody fragments, and antibody derivatives of the present invention.

- 15 For example, antibody fragments of the present invention can be produced in *Pichia pastoris* and in *Saccharomyces cerevisiae*. *See, e.g.*, Takahashi *et al.*, *Biosci. Biotechnol. Biochem.* 64(10): 2138-44 (2000); Freyre *et al.*, *J. Biotechnol.* 76(2-3):1 57-63 (2000); Fischer *et al.*, *Biotechnol. Appl. Biochem.* 30 (Pt 2): 117-20 (1999); Pennell *et al.*, *Res. Immunol.* 149(6): 599-603 (1998); Eldin *et al.*, *J. Immunol. Methods.* 201(1): 67-75 (1997);, Frenken *et al.*, *Res. Immunol.* 149(6): 589-99 (1998); Shusta *et al.*, *Nature Biotechnol.* 16(8): 773-7 (1998), the disclosures of which are incorporated herein by reference in their entireties.

- Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in insect cells. *See, e.g.*, Li *et al.*, *Protein Expr. Purif.*
25 21(1): 121-8 (2001); Ailor *et al.*, *Biotechnol. Bioeng.* 58(2-3): 196-203 (1998); Hsu *et al.*, *Biotechnol. Prog.* 13(1): 96-104 (1997); Edelman *et al.*, *Immunology* 91(1): 13-9 (1997); and Nesbit *et al.*, *J. Immunol. Methods* 151(1-2): 201-8 (1992), the disclosures of which are incorporated herein by reference in their entireties.

- Antibodies and fragments and derivatives thereof of the present invention can
30 also be produced in plant cells, particularly maize or tobacco, Giddings *et al.*, *Nature Biotechnol.* 18(11): 1151-5 (2000); Gavilondo *et al.*, *Biotechniques* 29(1): 128-38 (2000); Fischer *et al.*, *J. Biol. Regul. Homeost. Agents* 14(2): 83-92 (2000); Fischer *et al.*,

Biotechnol. Appl. Biochem. 30 (Pt 2): 113-6 (1999); Fischer *et al.*, *Biol. Chem.* 380(7-8): 825-39 (1999); Russell, *Curr. Top. Microbiol. Immunol.* 240: 119-38 (1999); and Ma *et al.*, *Plant Physiol.* 109(2): 341-6 (1995), the disclosures of which are incorporated herein by reference in their entirety.

5 Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in transgenic, non-human, mammalian milk. *See, e.g.* Pollock *et al.*, *J. Immunol. Methods.* 231: 147-57 (1999); Young *et al.*, *Res. Immunol.* 149: 609-10 (1998); Limonta *et al.*, *Immunotechnology* 1: 107-13 (1995), the disclosures of which are incorporated herein by reference in their entirety.

10 Mammalian cells useful for recombinant expression of antibodies, antibody fragments, and antibody derivatives of the present invention include CHO cells, COS cells, 293 cells, and myeloma cells.

 Verma *et al.*, *J. Immunol. Methods* 216(1-2):165-81 (1998), herein incorporated by reference, review and compare bacterial, yeast, insect and mammalian expression
15 systems for expression of antibodies.

 Antibodies of the present invention can also be prepared by cell free translation, as further described in Merk *et al.*, *J. Biochem. (Tokyo)* 125(2): 328-33 (1999) and Ryabova *et al.*, *Nature Biotechnol.* 15(1): 79-84 (1997), and in the milk of transgenic animals, as further described in Pollock *et al.*, *J. Immunol. Methods* 231(1-2): 147-57
20 (1999), the disclosures of which are incorporated herein by reference in their entirety.

 The invention further provides antibody fragments that bind specifically to one or more of the proteins and protein fragments of the present invention, to one or more of the proteins and protein fragments encoded by the isolated nucleic acids of the present invention, or the binding of which can be competitively inhibited by one or more of the
25 proteins and protein fragments of the present invention or one or more of the proteins and protein fragments encoded by the isolated nucleic acids of the present invention.

 Among such useful fragments are Fab, Fab', Fv, F(ab)'₂, and single chain Fv (scFv) fragments. Other useful fragments are described in Hudson, *Curr. Opin. Biotechnol.* 9(4): 395-402 (1998).

30 It is also an aspect of the present invention to provide antibody derivatives that bind specifically to one or more of the proteins and protein fragments of the present invention, to one or more of the proteins and protein fragments encoded by the isolated

nucleic acids of the present invention, or the binding of which can be competitively inhibited by one or more of the proteins and protein fragments of the present invention or one or more of the proteins and protein fragments encoded by the isolated nucleic acids of the present invention.

5 Among such useful derivatives are chimeric, primatized, and humanized antibodies; such derivatives are less immunogenic in human beings, and thus more suitable for *in vivo* administration, than are unmodified antibodies from non-human mammalian species. Another useful derivative is PEGylation to increase the serum half life of the antibodies.

10 Chimeric antibodies typically include heavy and/or light chain variable regions (including both CDR and framework residues) of immunoglobulins of one species, typically mouse, fused to constant regions of another species, typically human. *See, e.g.*, United States Patent No. 5,807,715; Morrison *et al.*, *Proc. Natl. Acad. Sci USA* 81(21): 6851-5 (1984); Sharon *et al.*, *Nature* 309(5966): 364-7 (1984); Takeda *et al.*, *Nature*
15 314(6010): 452-4 (1985), the disclosures of which are incorporated herein by reference in their entireties. Primatized and humanized antibodies typically include heavy and/or light chain CDRs from a murine antibody grafted into a non-human primate or human antibody V region framework, usually further comprising a human constant region, Riechmann *et al.*, *Nature* 332(6162): 323-7 (1988); Co *et al.*, *Nature* 351(6326): 501-2
20 (1991); United States Patent Nos. 6,054,297; 5,821,337; 5,770,196; 5,766,886; 5,821,123; 5,869,619; 6,180,377; 6,013,256; 5,693,761; and 6,180,370, the disclosures of which are incorporated herein by reference in their entireties.

Other useful antibody derivatives of the invention include heteromeric antibody complexes and antibody fusions, such as diabodies (bispecific antibodies), single-chain
25 diabodies, and intrabodies.

It is contemplated that the nucleic acids encoding the antibodies of the present invention can be operably joined to other nucleic acids forming a recombinant vector for cloning or for expression of the antibodies of the invention. The present invention includes any recombinant vector containing the coding sequences, or part thereof,
30 whether for eukaryotic transduction, transfection or gene therapy. Such vectors may be prepared using conventional molecular biology techniques, known to those with skill in the art, and would comprise DNA encoding sequences for the immunoglobulin V-regions

including framework and CDRs or parts thereof, and a suitable promoter either with or without a signal sequence for intracellular transport. Such vectors may be transduced or transfected into eukaryotic cells or used for gene therapy (Marasco et al., *Proc. Natl. Acad. Sci. (USA)* 90: 7889-7893 (1993); Duan et al., *Proc. Natl. Acad. Sci. (USA)* 91: 5075-5079 (1994), by conventional techniques, known to those with skill in the art.

The antibodies of the present invention, including fragments and derivatives thereof, can usefully be labeled. It is, therefore, another aspect of the present invention to provide labeled antibodies that bind specifically to one or more of the proteins and protein fragments of the present invention, to one or more of the proteins and protein fragments encoded by the isolated nucleic acids of the present invention, or the binding of which can be competitively inhibited by one or more of the proteins and protein fragments of the present invention or one or more of the proteins and protein fragments encoded by the isolated nucleic acids of the present invention.

The choice of label depends, in part, upon the desired use.

For example, when the antibodies of the present invention are used for immunohistochemical staining of tissue samples, the label is preferably an enzyme that catalyzes production and local deposition of a detectable product.

Enzymes typically conjugated to antibodies to permit their immunohistochemical visualization are well-known, and include alkaline phosphatase, β -galactosidase, glucose oxidase, horseradish peroxidase (HRP), and urease. Typical substrates for production and deposition of visually detectable products include o-nitrophenyl-beta-D-galactopyranoside (ONPG); o-phenylenediamine dihydrochloride (OPD); p-nitrophenyl phosphate (PNPP); p-nitrophenyl-beta-D-galactopyranoside (PNPG); 3',3'-diaminobenzidine (DAB); 3-amino-9-ethylcarbazole (AEC); 4-chloro-1-naphthol (CN); 5-bromo-4-chloro-3-indolyl-phosphate (BCIP); ABTS®; BluoGal; iodonitrotetrazolium (INT); nitroblue tetrazolium chloride (NBT); phenazine methosulfate (PMS); phenolphthalein monophosphate (PMP); tetramethyl benzidine (TMB); tetranitroblue tetrazolium (TNBT); X-Gal; X-Gluc; and X-Glucoside.

Other substrates can be used to produce products for local deposition that are luminescent. For example, in the presence of hydrogen peroxide (H_2O_2), horseradish peroxidase (HRP) can catalyze the oxidation of cyclic diacylhydrazides, such as luminol. Immediately following the oxidation, the luminol is in an excited state (intermediate

reaction product), which decays to the ground state by emitting light. Strong enhancement of the light emission is produced by enhancers, such as phenolic compounds. Advantages include high sensitivity, high resolution, and rapid detection without radioactivity and requiring only small amounts of antibody. See, e.g., Thorpe *et al.*, *Methods Enzymol.* 133: 331-53 (1986); Kricka *et al.*, *J. Immunoassay* 17(1): 67-83 (1996); and Lundqvist *et al.*, *J. Biolumin. Chemilumin.* 10(6): 353-9 (1995), the disclosures of which are incorporated herein by reference in their entireties. Kits for such enhanced chemiluminescent detection (ECL) are available commercially.

The antibodies can also be labeled using colloidal gold.

10 As another example, when the antibodies of the present invention are used, e.g., for flow cytometric detection, for scanning laser cytometric detection, or for fluorescent immunoassay, they can usefully be labeled with fluorophores.

There are a wide variety of fluorophore labels that can usefully be attached to the antibodies of the present invention.

15 For flow cytometric applications, both for extracellular detection and for intracellular detection, common useful fluorophores can be fluorescein isothiocyanate (FITC), allophycocyanin (APC), R-phycoerythrin (PE), peridinin chlorophyll protein (PerCP), Texas Red, Cy3, Cy5, fluorescence resonance energy tandem fluorophores such as PerCP-Cy5.5, PE-Cy5, PE-Cy5.5, PE-Cy7, PE-Texas Red, and APC-Cy7.

20 Other fluorophores include, *inter alia*, Alexa Fluor® 350, Alexa Fluor® 488, Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc., Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, BODIPY 558/568,
25 BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY TR, BODIPY 630/650, BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B, Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from Molecular Probes, Inc., Eugene, OR, USA), and Cy2, Cy3, Cy3.5, Cy5,
30 Cy5.5, Cy7, all of which are also useful for fluorescently labeling the antibodies of the present invention.

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For secondary detection using labeled avidin, streptavidin, captavidin or neutravidin, the antibodies of the present invention can usefully be labeled with biotin.

When the antibodies of the present invention are used, *e.g.*, for Western blotting applications, they can usefully be labeled with radioisotopes, such as ^{33}P , ^{32}P , ^{35}S , ^3H ,
5 and ^{125}I .

As another example, when the antibodies of the present invention are used for radioimmunotherapy, the label can usefully be ^{228}Th , ^{227}Ac , ^{225}Ac , ^{223}Ra , ^{213}Bi , ^{212}Pb , ^{212}Bi , ^{211}At , ^{203}Pb , ^{194}Os , ^{188}Re , ^{186}Re , ^{153}Sm , ^{149}Tb , ^{131}I , ^{125}I , ^{111}In , ^{105}Rh , $^{99\text{m}}\text{Tc}$, ^{97}Ru , ^{90}Y , ^{90}Sr , ^{88}Y , ^{72}Se , ^{67}Cu , or ^{47}Sc .

10 As another example, when the antibodies of the present invention are to be used for *in vivo* diagnostic use, they can be rendered detectable by conjugation to MRI contrast agents, such as gadolinium diethylenetriaminepentaacetic acid (DTPA), Lauffer *et al.*, *Radiology* 207(2): 529-38 (1998), or by radioisotopic labeling.

As would be understood, use of the labels described above is not restricted to the
15 application for which they are mentioned.

The antibodies of the present invention, including fragments and derivatives thereof, can also be conjugated to toxins, in order to target the toxin's ablative action to cells that display and/or express the proteins of the present invention. Commonly, the antibody in such immunotoxins is conjugated to *Pseudomonas* exotoxin A, *diphtheria*
20 toxin, *shiga* toxin A, *anthrax* toxin lethal factor, or ricin. See Hall (ed.), Immunotoxin Methods and Protocols (Methods in Molecular Biology, vol. 166), Humana Press (2000); and Frankel *et al.* (eds.), Clinical Applications of Immunotoxins, Springer-Verlag (1998), the disclosures of which are incorporated herein by reference in their entireties.

The antibodies of the present invention can usefully be attached to a substrate,
25 and it is, therefore, another aspect of the invention to provide antibodies that bind specifically to one or more of the proteins and protein fragments of the present invention, to one or more of the proteins and protein fragments encoded by the isolated nucleic acids of the present invention, or the binding of which can be competitively inhibited by one or more of the proteins and protein fragments of the present invention or one or more
30 of the proteins and protein fragments encoded by the isolated nucleic acids of the present invention, attached to a substrate.

Substrates can be porous or nonporous, planar or nonplanar.

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For example, the antibodies of the present invention can usefully be conjugated to filtration media, such as NHS-activated Sepharose or CNBr-activated Sepharose for purposes of immunoaffinity chromatography.

For example, the antibodies of the present invention can usefully be attached to
5 paramagnetic microspheres, typically by biotin-streptavidin interaction, which microspheres can then be used for isolation of cells that express or display the proteins of the present invention. As another example, the antibodies of the present invention can usefully be attached to the surface of a microtiter plate for ELISA.

As noted above, the antibodies of the present invention can be produced in
10 prokaryotic and eukaryotic cells. It is, therefore, another aspect of the present invention to provide cells that express the antibodies of the present invention, including hybridoma cells, B cells, plasma cells, and host cells recombinantly modified to express the antibodies of the present invention.

In yet a further aspect, the present invention provides aptamers evolved to bind
15 specifically to one or more of the proteins and protein fragments of the present invention, to one or more of the proteins and protein fragments encoded by the isolated nucleic acids of the present invention, or the binding of which can be competitively inhibited by one or more of the proteins and protein fragments of the present invention or one or more of the proteins and protein fragments encoded by the isolated nucleic acids of the present
20 invention.

In sum, one of skill in the art, provided with the teachings of this invention, has available a variety of methods which may be used to alter the biological properties of the antibodies of this invention including methods which would increase or decrease the stability or half-life, immunogenicity, toxicity, affinity or yield of a given antibody
25 molecule, or to alter it in any other way that may render it more suitable for a particular application.

Transgenic Animals and Cells

In another aspect, the invention provides transgenic cells and non-human
30 organisms comprising nucleic acid molecules of the invention. In a preferred embodiment, the transgenic cells and non-human organisms comprise a nucleic acid molecule encoding a BSP. In a preferred embodiment, the BSP comprises an amino acid

sequence selected from SEQ ID NO: 165 through 280, or a fragment, mutein, homologous protein or allelic variant thereof. In another preferred embodiment, the transgenic cells and non-human organism comprise a BSNA of the invention, preferably a BSNA comprising a nucleotide sequence selected from the group consisting of SEQ ID
5 NO: 1 through 164, or a part, substantially similar nucleic acid molecule, allelic variant or hybridizing nucleic acid molecule thereof.

In another embodiment, the transgenic cells and non-human organisms have a targeted disruption or replacement of the endogenous orthologue of the human BSG. The transgenic cells can be embryonic stem cells or somatic cells. The transgenic non-
10 human organisms can be chimeric, nonchimeric heterozygotes, and nonchimeric homozygotes. Methods of producing transgenic animals are well-known in the art. *See, e.g., Hogan et al., Manipulating the Mouse Embryo: A Laboratory Manual*, 2d ed., Cold Spring Harbor Press (1999); Jackson *et al.*, *Mouse Genetics and Transgenics: A Practical Approach*, Oxford University Press (2000); and Pinkert, *Transgenic Animal Technology: A Laboratory Handbook*, Academic Press (1999).
15

Any technique known in the art may be used to introduce a nucleic acid molecule of the invention into an animal to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection. (*see, e.g., Paterson et al., Appl. Microbiol. Biotechnol.* 40: 691-698 (1994); Carver *et al.*, *Biotechnology* 11: 1263-1270 (1993); Wright *et al.*, *Biotechnology* 9: 830-834 (1991); and U.S. Patent 4,873,191 (1989 retrovirus-mediated gene transfer into germ lines, blastocysts or embryos (*see, e.g., Van der Putten et al., Proc. Natl. Acad. Sci., USA* 82: 6148-6152 (1985)); gene targeting in embryonic stem cells (*see, e.g., Thompson et al., Cell* 56: 313-321 (1989)); electroporation of cells or embryos (*see, e.g., Lo, 1983, Mol. Cell. Biol.* 3: 1803-1814 (1983)); introduction using a gene gun (*see, e.g., Ulmer et al., Science* 259: 1745-49 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (*see, e.g., Lavitrano et al., Cell* 57: 717-723 (1989)).
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25

Other techniques include, for example, nuclear transfer into enucleated oocytes of
30 nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (*see, e.g., Campell et al., Nature* 380: 64-66 (1996); Wilmut *et al.*, *Nature* 385: 810-813 (1997)). The present invention provides for transgenic animals that carry the transgene (*i.e., a*

nucleic acid molecule of the invention) in all their cells, as well as animals which carry the transgene in some, but not all their cells, i. e., mosaic animals or chimeric animals.

The transgene may be integrated as a single transgene or as multiple copies, such as in concatamers, e. g., head-to-head tandems or head-to-tail tandems. The transgene
5 may also be selectively introduced into and activated in a particular cell type by following, e.g., the teaching of Lasko *et al. et al.*, *Proc. Natl. Acad. Sci. USA* 89: 6232-6236 (1992). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

10 Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using
15 techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (RT-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

20 Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels
25 because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is
30 appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of

the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Methods for creating a transgenic animal with a disruption of a targeted gene are also well-known in the art. In general, a vector is designed to comprise some nucleotide sequences homologous to the endogenous targeted gene. The vector is introduced into a cell so that it may integrate, via homologous recombination with chromosomal sequences, into the endogenous gene, thereby disrupting the function of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type. *See, e.g., Gu et al., Science* 265: 103-106 (1994). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. *See, e.g., Smithies et al., Nature* 317: 230-234 (1985); Thomas *et al., Cell* 51: 503-512 (1987); Thompson *et al., Cell* 5: 313-321 (1989).

In one embodiment, a mutant, non-functional nucleic acid molecule of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous nucleic acid sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene. *See, e.g., Thomas, supra* and Thompson, *supra*. However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g., knockouts*) are administered to a patient *in vivo*. Such cells may be obtained from an animal or patient or an MHC

compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt
5 the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

10 The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

15 Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. *See, e.g.*, U.S. Patents 5,399,349 and 5,460,959, each of which is incorporated by reference herein in its entirety.

20 When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well-known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the
25 introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such
30 conditions and/or disorders.

Computer Readable Means

A further aspect of the invention relates to a computer readable means for storing the nucleic acid and amino acid sequences of the instant invention. In a preferred embodiment, the invention provides a computer readable means for storing SEQ ID NO: 1 through 164 and SEQ ID NO: 165 through 280 as described herein, as the complete set of sequences or in any combination. The records of the computer readable means can be accessed for reading and display and for interface with a computer system for the application of programs allowing for the location of data upon a query for data meeting certain criteria, the comparison of sequences, the alignment or ordering of sequences meeting a set of criteria, and the like.

The nucleic acid and amino acid sequences of the invention are particularly useful as components in databases useful for search analyses as well as in sequence analysis algorithms. As used herein, the terms "nucleic acid sequences of the invention" and "amino acid sequences of the invention" mean any detectable chemical or physical characteristic of a polynucleotide or polypeptide of the invention that is or may be reduced to or stored in a computer readable form. These include, without limitation, chromatographic scan data or peak data, photographic data or scan data therefrom, and mass spectrographic data.

This invention provides computer readable media having stored thereon sequences of the invention. A computer readable medium may comprise one or more of the following: a nucleic acid sequence comprising a sequence of a nucleic acid sequence of the invention; an amino acid sequence comprising an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said sequences comprises the sequence of a nucleic acid sequence of the invention; a set of amino acid sequences wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention; a data set representing a nucleic acid sequence comprising the sequence of one or more nucleic acid sequences of the invention; a data set representing a nucleic acid sequence encoding an amino acid sequence comprising the sequence of an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said sequences comprises the sequence of a nucleic acid sequence of the invention; a set of amino acid sequences wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention; a data set

representing a nucleic acid sequence comprising the sequence of a nucleic acid sequence of the invention; a data set representing a nucleic acid sequence encoding an amino acid sequence comprising the sequence of an amino acid sequence of the invention. The computer readable medium can be any composition of matter used to store information or data, including, for example, commercially available floppy disks, tapes, hard drives, compact disks, and video disks.

Also provided by the invention are methods for the analysis of character sequences, particularly genetic sequences. Preferred methods of sequence analysis include, for example, methods of sequence homology analysis, such as identity and similarity analysis, RNA structure analysis, sequence assembly, cladistic analysis, sequence motif analysis, open reading frame determination, nucleic acid base calling, and sequencing chromatogram peak analysis.

A computer-based method is provided for performing nucleic acid sequence identity or similarity identification. This method comprises the steps of providing a nucleic acid sequence comprising the sequence of a nucleic acid of the invention in a computer readable medium; and comparing said nucleic acid sequence to at least one nucleic acid or amino acid sequence to identify sequence identity or similarity.

A computer-based method is also provided for performing amino acid homology identification, said method comprising the steps of: providing an amino acid sequence comprising the sequence of an amino acid of the invention in a computer readable medium; and comparing said an amino acid sequence to at least one nucleic acid or an amino acid sequence to identify homology.

A computer-based method is still further provided for assembly of overlapping nucleic acid sequences into a single nucleic acid sequence, said method comprising the steps of: providing a first nucleic acid sequence comprising the sequence of a nucleic acid of the invention in a computer readable medium; and screening for at least one overlapping region between said first nucleic acid sequence and a second nucleic acid sequence.

Diagnostic Methods for Breast Cancer

The present invention also relates to quantitative and qualitative diagnostic assays and methods for detecting, diagnosing, monitoring, staging and predicting cancers by

comparing expression of a BSNA or a BSP in a human patient that has or may have breast cancer, or who is at risk of developing breast cancer, with the expression of a BSNA or a BSP in a normal human control. For purposes of the present invention, “expression of a BSNA” or “BSNA expression” means the quantity of BSG mRNA that
5 can be measured by any method known in the art or the level of transcription that can be measured by any method known in the art in a cell, tissue, organ or whole patient. Similarly, the term “expression of a BSP” or “BSP expression” means the amount of BSP that can be measured by any method known in the art or the level of translation of a BSG BSNA that can be measured by any method known in the art.

10 The present invention provides methods for diagnosing breast cancer in a patient, in particular squamous cell carcinoma, by analyzing for changes in levels of BSNA or BSP in cells, tissues, organs or bodily fluids compared with levels of BSNA or BSP in cells, tissues, organs or bodily fluids of preferably the same type from a normal human control, wherein an increase, or decrease in certain cases, in levels of a BSNA or BSP in
15 the patient versus the normal human control is associated with the presence of breast cancer or with a predilection to the disease. In another preferred embodiment, the present invention provides methods for diagnosing breast cancer in a patient by analyzing changes in the structure of the mRNA of a BSG compared to the mRNA from a normal control. These changes include, without limitation, aberrant splicing, alterations in
20 polyadenylation and/or alterations in 5’ nucleotide capping. In yet another preferred embodiment, the present invention provides methods for diagnosing breast cancer in a patient by analyzing changes in a BSP compared to a BSP from a normal control. These changes include, *e.g.*, alterations in glycosylation and/or phosphorylation of the BSP or subcellular BSP localization.

25 In a preferred embodiment, the expression of a BSNA is measured by determining the amount of an mRNA that encodes an amino acid sequence selected from SEQ ID NO: 165 through 280, a homolog, an allelic variant, or a fragment thereof. In a more preferred embodiment, the BSNA expression that is measured is the level of expression of a BSNA mRNA selected from SEQ ID NO: 1 through 164, or a
30 hybridizing nucleic acid, homologous nucleic acid or allelic variant thereof, or a part of any of these nucleic acids. BSNA expression may be measured by any method known in the art, such as those described *supra*, including measuring mRNA expression by

Northern blot, quantitative or qualitative reverse transcriptase PCR (RT-PCR), microarray, dot or slot blots or *in situ* hybridization. *See, e.g.,* Ausubel (1992), *supra*; Ausubel (1999), *supra*; Sambrook (1989), *supra*; and Sambrook (2001), *supra*. BSNA transcription may be measured by any method known in the art including using a reporter
5 gene hooked up to the promoter of a BSG of interest or doing nuclear run-off assays. Alterations in mRNA structure, *e.g.,* aberrant splicing variants, may be determined by any method known in the art, including, RT-PCR followed by sequencing or restriction analysis. As necessary, BSNA expression may be compared to a known control, such as normal breast nucleic acid, to detect a change in expression.

10 In another preferred embodiment, the expression of a BSP is measured by determining the level of a BSP having an amino acid sequence selected from the group consisting of SEQ ID NO: 165 through 280, a homolog, an allelic variant, or a fragment thereof. Such levels are preferably determined in at least one of cells, tissues, organs and/or bodily fluids, including determination of normal and abnormal levels. Thus, for
15 instance, a diagnostic assay in accordance with the invention for diagnosing over- or underexpression of BSNA or BSP compared to normal control bodily fluids, cells, or tissue samples may be used to diagnose the presence of breast cancer. The expression level of a BSP may be determined by any method known in the art, such as those described *supra*. In a preferred embodiment, the BSP expression level may be
20 determined by radioimmunoassays, competitive-binding assays, ELISA, Western blot, FACS, immunohistochemistry, immunoprecipitation, proteomic approaches: two-dimensional gel electrophoresis (2D electrophoresis) and non-gel-based approaches such as mass spectrometry or protein interaction profiling. *See, e.g.,* Harlow (1999), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. Alterations in the BSP
25 structure may be determined by any method known in the art, including, *e.g.,* using antibodies that specifically recognize phosphoserine, phosphothreonine or phosphotyrosine residues, two-dimensional polyacrylamide gel electrophoresis (2D PAGE) and/or chemical analysis of amino acid residues of the protein. *Id.*

In a preferred embodiment, a radioimmunoassay (RIA) or an ELISA is used. An
30 antibody specific to a BSP is prepared if one is not already available. In a preferred embodiment, the antibody is a monoclonal antibody. The anti-BSP antibody is bound to a solid support and any free protein binding sites on the solid support are blocked with a

protein such as bovine serum albumin. A sample of interest is incubated with the antibody on the solid support under conditions in which the BSP will bind to the anti-BSP antibody. The sample is removed, the solid support is washed to remove unbound material, and an anti-BSP antibody that is linked to a detectable reagent (a radioactive
5 substance for RIA and an enzyme for ELISA) is added to the solid support and incubated under conditions in which binding of the BSP to the labeled antibody will occur. After binding, the unbound labeled antibody is removed by washing. For an ELISA, one or more substrates are added to produce a colored reaction product that is based upon the amount of a BSP in the sample. For an RIA, the solid support is counted for radioactive
10 decay signals by any method known in the art. Quantitative results for both RIA and ELISA typically are obtained by reference to a standard curve.

Other methods to measure BSP levels are known in the art. For instance, a competition assay may be employed wherein an anti-BSP antibody is attached to a solid support and an allocated amount of a labeled BSP and a sample of interest are incubated
15 with the solid support. The amount of labeled BSP detected which is attached to the solid support can be correlated to the quantity of a BSP in the sample.

Of the proteomic approaches, 2D PAGE is a well-known technique. Isolation of individual proteins from a sample such as serum is accomplished using sequential separation of proteins by isoelectric point and molecular weight. Typically, polypeptides
20 are first separated by isoelectric point (the first dimension) and then separated by size using an electric current (the second dimension). In general, the second dimension is perpendicular to the first dimension. Because no two proteins with different sequences are identical on the basis of both size and charge, the result of 2D PAGE is a roughly square gel in which each protein occupies a unique spot. Analysis of the spots with
25 chemical or antibody probes, or subsequent protein microsequencing can reveal the relative abundance of a given protein and the identity of the proteins in the sample.

Expression levels of a BSNA can be determined by any method known in the art, including PCR and other nucleic acid methods, such as ligase chain reaction (LCR) and nucleic acid sequence based amplification (NASBA), can be used to detect malignant
30 cells for diagnosis and monitoring of various malignancies. For example, reverse-transcriptase PCR (RT-PCR) is a powerful technique which can be used to detect the presence of a specific mRNA population in a complex mixture of thousands of other

mRNA species. In RT-PCR, an mRNA species is first reverse transcribed to complementary DNA (cDNA) with use of the enzyme reverse transcriptase; the cDNA is then amplified as in a standard PCR reaction.

Hybridization to specific DNA molecules (*e.g.*, oligonucleotides) arrayed on a solid support can be used to both detect the expression of and quantitate the level of expression of one or more BSNAs of interest. In this approach, all or a portion of one or more BSNAs is fixed to a substrate. A sample of interest, which may comprise RNA, *e.g.*, total RNA or polyA-selected mRNA, or a complementary DNA (cDNA) copy of the RNA is incubated with the solid support under conditions in which hybridization will occur between the DNA on the solid support and the nucleic acid molecules in the sample of interest. Hybridization between the substrate-bound DNA and the nucleic acid molecules in the sample can be detected and quantitated by several means, including, without limitation, radioactive labeling or fluorescent labeling of the nucleic acid molecule or a secondary molecule designed to detect the hybrid.

The above tests can be carried out on samples derived from a variety of cells, bodily fluids and/or tissue extracts such as homogenates or solubilized tissue obtained from a patient. Tissue extracts are obtained routinely from tissue biopsy and autopsy material. Bodily fluids useful in the present invention include blood, urine, saliva or any other bodily secretion or derivative thereof. By blood it is meant to include whole blood, plasma, serum or any derivative of blood. In a preferred embodiment, the specimen tested for expression of BSNA or BSP includes, without limitation, breast tissue, fluid obtained by bronchial alveolar lavage (BAL), sputum, breast cells grown in cell culture, blood, serum, lymph node tissue and lymphatic fluid. In another preferred embodiment, especially when metastasis of a primary breast cancer is known or suspected, specimens include, without limitation, tissues from brain, bone, bone marrow, liver, adrenal glands and colon. In general, the tissues may be sampled by biopsy, including, without limitation, needle biopsy, *e.g.*, transthoracic needle aspiration, cervical mediastinoscopy, endoscopic lymph node biopsy, video-assisted thoracoscopy, exploratory thoracotomy, bone marrow biopsy and bone marrow aspiration. See Scott, *supra* and Franklin, pp. 529-570, in Kane, *supra*. For early and inexpensive detection, assaying for changes in BSNAs or BSPs in cells in sputum samples may be particularly useful. Methods of obtaining and analyzing sputum samples is disclosed in Franklin, *supra*.

All the methods of the present invention may optionally include determining the expression levels of one or more other cancer markers in addition to determining the expression level of a BSNA or BSP. In many cases, the use of another cancer marker will decrease the likelihood of false positives or false negatives. In one embodiment, the one or more other cancer markers include other BSNA or BSPs as disclosed herein. Other cancer markers useful in the present invention will depend on the cancer being tested and are known to those of skill in the art. In a preferred embodiment, at least one other cancer marker in addition to a particular BSNA or BSP is measured. In a more preferred embodiment, at least two other additional cancer markers are used. In an even more preferred embodiment, at least three, more preferably at least five, even more preferably at least ten additional cancer markers are used.

Diagnosing

In one aspect, the invention provides a method for determining the expression levels and/or structural alterations of one or more BSNAs and/or BSPs in a sample from a patient suspected of having breast cancer. In general, the method comprises the steps of obtaining the sample from the patient, determining the expression level or structural alterations of a BSNA and/or BSP and then ascertaining whether the patient has breast cancer from the expression level of the BSNA or BSP. In general, if high expression relative to a control of a BSNA or BSP is indicative of breast cancer, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least two times higher, and more preferably are at least five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a BSNA or BSP is indicative of breast cancer, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least two times lower, more preferably are at least five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

The present invention also provides a method of determining whether breast cancer has metastasized in a patient. One may identify whether the breast cancer has metastasized by measuring the expression levels and/or structural alterations of one or more BSNAs and/or BSPs in a variety of tissues. The presence of a BSNA or BSP in a

certain tissue at levels higher than that of corresponding noncancerous tissue (e.g., the same tissue from another individual) is indicative of metastasis if high level expression of a BSNA or BSP is associated with breast cancer. Similarly, the presence of a BSNA or BSP in a tissue at levels lower than that of corresponding noncancerous tissue is
5 indicative of metastasis if low level expression of a BSNA or BSP is associated with breast cancer. Further, the presence of a structurally altered BSNA or BSP that is associated with breast cancer is also indicative of metastasis.

In general, if high expression relative to a control of a BSNA or BSP is indicative of metastasis, an assay for metastasis is considered positive if the level of expression of
10 the BSNA or BSP is at least two times higher, and more preferably are at least five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a BSNA or BSP is indicative of metastasis, an assay for metastasis is
15 lower, more preferably are at least five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control.

The BSNA or BSP of this invention may be used as element in an array or a multi-analyte test to recognize expression patterns associated with breast cancers or other
20 breast related disorders. In addition, the sequences of either the nucleic acids or proteins may be used as elements in a computer program for pattern recognition of breast disorders.

Staging

25 The invention also provides a method of staging breast cancer in a human patient. The method comprises identifying a human patient having breast cancer and analyzing cells, tissues or bodily fluids from such human patient for expression levels and/or structural alterations of one or more BSNAs or BSPs. First, one or more tumors from a variety of patients are staged according to procedures well-known in the art, and the
30 expression level of one or more BSNAs or BSPs is determined for each stage to obtain a standard expression level for each BSNA and BSP. Then, the BSNA or BSP expression levels are determined in a biological sample from a patient whose stage of cancer is not

known. The BSNA or BSP expression levels from the patient are then compared to the standard expression level. By comparing the expression level of the BSNA and BSPs from the patient to the standard expression levels, one may determine the stage of the tumor. The same procedure may be followed using structural alterations of a BSNA or
5 BSP to determine the stage of a breast cancer.

Monitoring

Further provided is a method of monitoring breast cancer in a human patient. One may monitor a human patient to determine whether there has been metastasis and, if there has been, when metastasis began to occur. One may also monitor a human patient
10 to determine whether a preneoplastic lesion has become cancerous. One may also monitor a human patient to determine whether a therapy, *e.g.*, chemotherapy, radiotherapy or surgery, has decreased or eliminated the breast cancer. The method comprises identifying a human patient that one wants to monitor for breast cancer, periodically analyzing cells, tissues or bodily fluids from such human patient for
15 expression levels of one or more BSNA or BSPs, and comparing the BSNA or BSP levels over time to those BSNA or BSP expression levels obtained previously. Patients may also be monitored by measuring one or more structural alterations in a BSNA or BSP that are associated with breast cancer.

If increased expression of a BSNA or BSP is associated with metastasis,
20 treatment failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting an increase in the expression level of a BSNA or BSP indicates that the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. One having ordinary skill in the art would recognize that if this were the case, then a decreased expression level would be indicative of no metastasis, effective therapy or
25 failure to progress to a neoplastic lesion. If decreased expression of a BSNA or BSP is associated with metastasis, treatment failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting an decrease in the expression level of a BSNA or BSP indicates that the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. In a preferred embodiment, the levels of BSNA or BSPs are
30 determined from the same cell type, tissue or bodily fluid as prior patient samples. Monitoring a patient for onset of breast cancer metastasis is periodic and preferably is done on a quarterly basis, but may be done more or less frequently.

The methods described herein can further be utilized as prognostic assays to identify subjects having or at risk of developing a disease or disorder associated with increased or decreased expression levels of a BSNA and/or BSP. The present invention provides a method in which a test sample is obtained from a human patient and one or more BSNA and/or BSPs are detected. The presence of higher (or lower) BSNA or BSP levels as compared to normal human controls is diagnostic for the human patient being at risk for developing cancer, particularly breast cancer. The effectiveness of therapeutic agents to decrease (or increase) expression or activity of one or more BSNA and/or BSPs of the invention can also be monitored by analyzing levels of expression of the BSNA and/or BSPs in a human patient in clinical trials or in *in vitro* screening assays such as in human cells. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the human patient or cells, as the case may be, to the agent being tested.

Detection of Genetic Lesions or Mutations

The methods of the present invention can also be used to detect genetic lesions or mutations in a BSG, thereby determining if a human with the genetic lesion is susceptible to developing breast cancer or to determine what genetic lesions are responsible, or are partly responsible, for a person's existing breast cancer. Genetic lesions can be detected, for example, by ascertaining the existence of a deletion, insertion and/or substitution of one or more nucleotides from the BSGs of this invention, a chromosomal rearrangement of BSG, an aberrant modification of BSG (such as of the methylation pattern of the genomic DNA), or allelic loss of a BSG. Methods to detect such lesions in the BSG of this invention are known to those having ordinary skill in the art following the teachings of the specification.

Methods of Detecting Noncancerous Breast Diseases

The invention also provides a method for determining the expression levels and/or structural alterations of one or more BSNA and/or BSPs in a sample from a patient suspected of having or known to have a noncancerous breast disease. In general, the method comprises the steps of obtaining a sample from the patient, determining the expression level or structural alterations of a BSNA and/or BSP, comparing the expression level or structural alteration of the BSNA or BSP to a normal breast control,

and then ascertaining whether the patient has a noncancerous breast disease. In general, if high expression relative to a control of a BSNA or BSP is indicative of a particular noncancerous breast disease, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least two times higher, and more preferably are at least five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a BSNA or BSP is indicative of a noncancerous breast disease, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least two times lower, more preferably are at least five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

One having ordinary skill in the art may determine whether a BSNA and/or BSP is associated with a particular noncancerous breast disease by obtaining breast tissue from a patient having a noncancerous breast disease of interest and determining which BSNAs and/or BSPs are expressed in the tissue at either a higher or a lower level than in normal breast tissue. In another embodiment, one may determine whether a BSNA or BSP exhibits structural alterations in a particular noncancerous breast disease state by obtaining breast tissue from a patient having a noncancerous breast disease of interest and determining the structural alterations in one or more BSNAs and/or BSPs relative to normal breast tissue.

Methods for Identifying Breast Tissue

In another aspect, the invention provides methods for identifying breast tissue. These methods are particularly useful in, *e.g.*, forensic science, breast cell differentiation and development, and in tissue engineering.

In one embodiment, the invention provides a method for determining whether a sample is breast tissue or has breast tissue-like characteristics. The method comprises the steps of providing a sample suspected of comprising breast tissue or having breast tissue-like characteristics, determining whether the sample expresses one or more BSNAs and/or BSPs, and, if the sample expresses one or more BSNAs and/or BSPs, concluding that the sample comprises breast tissue. In a preferred embodiment, the BSNA encodes a

polypeptide having an amino acid sequence selected from SEQ ID NO: 165 through 280, or a homolog, allelic variant or fragment thereof. In a more preferred embodiment, the BSNA has a nucleotide sequence selected from SEQ ID NO: 1 through 164, or a hybridizing nucleic acid, an allelic variant or a part thereof. Determining whether a sample expresses a BSNA can be accomplished by any method known in the art. Preferred methods include hybridization to microarrays, Northern blot hybridization, and quantitative or qualitative RT-PCR. In another preferred embodiment, the method can be practiced by determining whether a BSP is expressed. Determining whether a sample expresses a BSP can be accomplished by any method known in the art. Preferred methods include Western blot, ELISA, RIA and 2D PAGE. In one embodiment, the BSP has an amino acid sequence selected from SEQ ID NO: 165 through 280, or a homolog, allelic variant or fragment thereof. In another preferred embodiment, the expression of at least two BSNA and/or BSPs is determined. In a more preferred embodiment, the expression of at least three, more preferably four and even more preferably five BSNA and/or BSPs are determined.

In one embodiment, the method can be used to determine whether an unknown tissue is breast tissue. This is particularly useful in forensic science, in which small, damaged pieces of tissues that are not identifiable by microscopic or other means are recovered from a crime or accident scene. In another embodiment, the method can be used to determine whether a tissue is differentiating or developing into breast tissue. This is important in monitoring the effects of the addition of various agents to cell or tissue culture, *e.g.*, in producing new breast tissue by tissue engineering. These agents include, *e.g.*, growth and differentiation factors, extracellular matrix proteins and culture medium. Other factors that may be measured for effects on tissue development and differentiation include gene transfer into the cells or tissues, alterations in pH, aqueous:air interface and various other culture conditions.

Methods for Producing and Modifying Breast Tissue

In another aspect, the invention provides methods for producing engineered breast tissue or cells. In one embodiment, the method comprises the steps of providing cells, introducing a BSNA or a BSG into the cells, and growing the cells under conditions in which they exhibit one or more properties of breast tissue cells. In a preferred

embodiment, the cells are pluripotent. As is well-known in the art, normal breast tissue comprises a large number of different cell types. Thus, in one embodiment, the engineered breast tissue or cells comprises one of these cell types. In another embodiment, the engineered breast tissue or cells comprises more than one breast cell type. Further, the culture conditions of the cells or tissue may require manipulation in order to achieve full differentiation and development of the breast cell tissue. Methods for manipulating culture conditions are well-known in the art.

Nucleic acid molecules encoding one or more BSPs are introduced into cells, preferably pluripotent cells. In a preferred embodiment, the nucleic acid molecules encode BSPs having amino acid sequences selected from SEQ ID NO: 165 through 280, or homologous proteins, analogs, allelic variants or fragments thereof. In a more preferred embodiment, the nucleic acid molecules have a nucleotide sequence selected from SEQ ID NO: 1 through 164, or hybridizing nucleic acids, allelic variants or parts thereof. In another highly preferred embodiment, a BSG is introduced into the cells. Expression vectors and methods of introducing nucleic acid molecules into cells are well-known in the art and are described in detail, *supra*.

Artificial breast tissue may be used to treat patients who have lost some or all of their breast function.

Pharmaceutical Compositions

In another aspect, the invention provides pharmaceutical compositions comprising the nucleic acid molecules, polypeptides, antibodies, antibody derivatives, antibody fragments, agonists, antagonists, and inhibitors of the present invention. In a preferred embodiment, the pharmaceutical composition comprises a BSNA or part thereof. In a more preferred embodiment, the BSNA has a nucleotide sequence selected from the group consisting of SEQ ID NO: 1 through 164, a nucleic acid that hybridizes thereto, an allelic variant thereof, or a nucleic acid that has substantial sequence identity thereto. In another preferred embodiment, the pharmaceutical composition comprises a BSP or fragment thereof. In a more preferred embodiment, the BSP having an amino acid sequence that is selected from the group consisting of SEQ ID NO: 165 through 280, a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or an analog or derivative thereof. In another preferred embodiment, the

pharmaceutical composition comprises an anti-BSP antibody, preferably an antibody that specifically binds to a BSP having an amino acid that is selected from the group consisting of SEQ ID NO: 165 through 280, or an antibody that binds to a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or an analog or derivative thereof.

Such a composition typically contains from about 0.1 to 90% by weight of a therapeutic agent of the invention formulated in and/or with a pharmaceutically acceptable carrier or excipient.

Pharmaceutical formulation is a well-established art, and is further described in Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20th ed., Lippincott, Williams & Wilkins (2000); Ansel *et al.*, Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., Lippincott Williams & Wilkins (1999); and Kibbe (ed.), Handbook of Pharmaceutical Excipients American Pharmaceutical Association, 3rd ed. (2000), the disclosures of which are incorporated herein by reference in their entireties, and thus need not be described in detail herein.

Briefly, formulation of the pharmaceutical compositions of the present invention will depend upon the route chosen for administration. The pharmaceutical compositions utilized in this invention can be administered by various routes including both enteral and parenteral routes, including oral, intravenous, intramuscular, subcutaneous, inhalation, topical, sublingual, rectal, intra-arterial, intramedullary, intrathecal, intraventricular, transmucosal, transdermal, intranasal, intraperitoneal, intrapulmonary, and intrauterine.

Oral dosage forms can be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Solid formulations of the compositions for oral administration can contain suitable carriers or excipients, such as carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or microcrystalline cellulose; gums including arabic and tragacanth; proteins such as gelatin and collagen; inorganics, such as kaolin, calcium carbonate, dicalcium phosphate, sodium chloride; and other agents such as acacia and alginic acid.

Agents that facilitate disintegration and/or solubilization can be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate, microcrystalline cellulose, corn starch, sodium starch glycolate, and alginic acid.

- 5 Tablet binders that can be used include acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone™), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose.

Lubricants that can be used include magnesium stearates, stearic acid, silicone fluid, talc, waxes, oils, and colloidal silica.

- 10 Fillers, agents that facilitate disintegration and/or solubilization, tablet binders and lubricants, including the aforementioned, can be used singly or in combination.

- Solid oral dosage forms need not be uniform throughout. For example, dragee cores can be used in conjunction with suitable coatings, such as concentrated sugar solutions, which can also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.
- 15

- Oral dosage forms of the present invention include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.
- 20

- Additionally, dyestuffs or pigments can be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, *i.e.*, dosage.
- 25

- Liquid formulations of the pharmaceutical compositions for oral (enteral) administration are prepared in water or other aqueous vehicles and can contain various suspending agents such as methylcellulose, alginates, tragacanth, pectin, kelgin, carrageenan, acacia, polyvinylpyrrolidone, and polyvinyl alcohol. The liquid formulations can also include solutions, emulsions, syrups and elixirs containing, together with the active compound(s), wetting agents, sweeteners, and coloring and flavoring agents.
- 30

The pharmaceutical compositions of the present invention can also be formulated for parenteral administration. Formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions.

For intravenous injection, water soluble versions of the compounds of the present invention are formulated in, or if provided as a lyophilate, mixed with, a physiologically acceptable fluid vehicle, such as 5% dextrose ("D5"), physiologically buffered saline, 0.9% saline, Hanks' solution, or Ringer's solution. Intravenous formulations may include carriers, excipients or stabilizers including, without limitation, calcium, human serum albumin, citrate, acetate, calcium chloride, carbonate, and other salts.

10 Intramuscular preparations, *e.g.* a sterile formulation of a suitable soluble salt form of the compounds of the present invention, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution. Alternatively, a suitable insoluble form of the compound can be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil
15 base, such as an ester of a long chain fatty acid (*e.g.*, ethyl oleate), fatty oils such as sesame oil, triglycerides, or liposomes.

Parenteral formulations of the compositions can contain various carriers such as vegetable oils, dimethylacetamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols (glycerol, propylene glycol, liquid polyethylene
20 glycol, and the like).

Aqueous injection suspensions can also contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Non-lipid polycationic amino polymers can also be used for delivery. Optionally, the suspension can also contain suitable stabilizers or agents that increase the solubility of
25 the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical compositions of the present invention can also be formulated to permit injectable, long-term, deposition. Injectable depot forms may be made by forming microencapsulated matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature
30 of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot

injectable formulations are also prepared by entrapping the drug in microemulsions that are compatible with body tissues.

The pharmaceutical compositions of the present invention can be administered topically.

5 For topical use the compounds of the present invention can also be prepared in suitable forms to be applied to the skin, or mucus membranes of the nose and throat, and can take the form of lotions, creams, ointments, liquid sprays or inhalants, drops, tinctures, lozenges, or throat paints. Such topical formulations further can include chemical compounds such as dimethylsulfoxide (DMSO) to facilitate surface penetration
10 of the active ingredient. In other transdermal formulations, typically in patch-delivered formulations, the pharmaceutically active compound is formulated with one or more skin penetrants, such as 2-N-methyl-pyrrolidone (NMP) or Azone. A topical semi-solid ointment formulation typically contains a concentration of the active ingredient from about 1 to 20%, e.g., 5 to 10%, in a carrier such as a pharmaceutical cream base.

15 For application to the eyes or ears, the compounds of the present invention can be presented in liquid or semi-liquid form formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints or powders.

 For rectal administration the compounds of the present invention can be administered in the form of suppositories admixed with conventional carriers such as
20 cocoa butter, wax or other glyceride.

 Inhalation formulations can also readily be formulated. For inhalation, various powder and liquid formulations can be prepared. For aerosol preparations, a sterile formulation of the compound or salt form of the compound may be used in inhalers, such as metered dose inhalers, and nebulizers. Aerosolized forms may be especially useful for
25 treating respiratory disorders.

 Alternatively, the compounds of the present invention can be in powder form for reconstitution in the appropriate pharmaceutically acceptable carrier at the time of delivery.

 The pharmaceutically active compound in the pharmaceutical compositions of the
30 present invention can be provided as the salt of a variety of acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts

tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

After pharmaceutical compositions have been prepared, they are packaged in an appropriate container and labeled for treatment of an indicated condition.

- 5 The active compound will be present in an amount effective to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

A "therapeutically effective dose" refers to that amount of active ingredient, for example BSP polypeptide, fusion protein, or fragments thereof, antibodies specific for
10 BSP, agonists, antagonists or inhibitors of BSP, which ameliorates the signs or symptoms of the disease or prevents progression thereof; as would be understood in the medical arts, cure, although desired, is not required.

The therapeutically effective dose of the pharmaceutical agents of the present invention can be estimated initially by *in vitro* tests, such as cell culture assays, followed
15 by assay in model animals, usually mice, rats, rabbits, dogs, or pigs. The animal model can also be used to determine an initial preferred concentration range and route of administration.

For example, the ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population) can be determined in
20 one or more cell culture of animal model systems. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as LD50/ED50. Pharmaceutical compositions that exhibit large therapeutic indices are preferred.

The data obtained from cell culture assays and animal studies are used in formulating an initial dosage range for human use, and preferably provide a range of
25 circulating concentrations that includes the ED50 with little or no toxicity. After administration, or between successive administrations, the circulating concentration of active agent varies within this range depending upon pharmacokinetic factors well-known in the art, such as the dosage form employed, sensitivity of the patient, and the route of administration.

- 30 The exact dosage will be determined by the practitioner, in light of factors specific to the subject requiring treatment. Factors that can be taken into account by the practitioner include the severity of the disease state, general health of the subject, age,

weight, gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

5 Normal dosage amounts may vary from 0.1 to 100,000 micrograms, up to a total dose of about 1 g, depending upon the route of administration. Where the therapeutic agent is a protein or antibody of the present invention, the therapeutic protein or antibody agent typically is administered at a daily dosage of 0.01 mg to 30 mg/kg of body weight of the patient (*e.g.*, 1 mg/kg to 5 mg/kg). The pharmaceutical formulation can be
10 administered in multiple doses per day, if desired, to achieve the total desired daily dose.

Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells,
15 conditions, locations, etc.

Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the pharmaceutical formulation(s) of the present invention to the patient. The pharmaceutical compositions of the present invention can be administered alone, or in combination with other therapeutic agents or interventions.

20 Therapeutic Methods

The present invention further provides methods of treating subjects having defects in a gene of the invention, *e.g.*, in expression, activity, distribution, localization, and/or solubility, which can manifest as a disorder of breast function. As used herein,
25 "treating" includes all medically-acceptable types of therapeutic intervention, including palliation and prophylaxis (prevention) of disease. The term "treating" encompasses any improvement of a disease, including minor improvements. These methods are discussed below.

Gene Therapy and Vaccines

30 The isolated nucleic acids of the present invention can also be used to drive *in vivo* expression of the polypeptides of the present invention. *In vivo* expression can be driven from a vector, typically a viral vector, often a vector based upon a replication

incompetent retrovirus, an adenovirus, or an adeno-associated virus (AAV) , for purpose of gene therapy. *In vivo* expression can also be driven from signals endogenous to the nucleic acid or from a vector, often a plasmid vector, such as pVAX1 (Invitrogen, Carlsbad, CA, USA), for purpose of “naked” nucleic acid vaccination, as further
5 described in U.S. Patents 5,589,466; 5,679,647; 5,804,566; 5,830,877; 5,843,913; 5,880,104; 5,958,891; 5,985,847; 6,017,897; 6,110,898; and 6,204,250, the disclosures of which are incorporated herein by reference in their entireties. For cancer therapy, it is preferred that the vector also be tumor-selective. *See, e.g., Doronin et al., J. Virol.* 75: 3314-24 (2001).

10 In another embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising a nucleic acid of the present invention is administered. The nucleic acid can be delivered in a vector that drives expression of a BSP, fusion protein, or fragment thereof, or without such vector. Nucleic acid compositions that can drive expression of a BSP are
15 administered, for example, to complement a deficiency in the native BSP, or as DNA vaccines. Expression vectors derived from virus, replication deficient retroviruses, adenovirus, adeno-associated (AAV) virus, herpes virus, or vaccinia virus can be used as can plasmids. *See, e.g., Cid-Arregui, supra.* In a preferred embodiment, the nucleic acid molecule encodes a BSP having the amino acid sequence of SEQ ID NO: 165 through
20 280, or a fragment, fusion protein, allelic variant or homolog thereof.

In still other therapeutic methods of the present invention, pharmaceutical compositions comprising host cells that express a BSP, fusions, or fragments thereof can be administered. In such cases, the cells are typically autologous, so as to circumvent xenogeneic or allotypic rejection, and are administered to complement defects in BSP
25 production or activity. In a preferred embodiment, the nucleic acid molecules in the cells encode a BSP having the amino acid sequence of SEQ ID NO: 165 through 280, or a fragment, fusion protein, allelic variant or homolog thereof.

Antisense Administration

Antisense nucleic acid compositions, or vectors that drive expression of a BSP
30 antisense nucleic acid, are administered to downregulate transcription and/or translation of a BSP in circumstances in which excessive production, or production of aberrant protein, is the pathophysiologic basis of disease.

Antisense compositions useful in therapy can have a sequence that is complementary to coding or to noncoding regions of a BSG. For example, oligonucleotides derived from the transcription initiation site, *e.g.*, between positions -10 and +10 from the start site, are preferred.

5 Catalytic antisense compositions, such as ribozymes, that are capable of sequence-specific hybridization to BSG transcripts, are also useful in therapy. *See, e.g.*, Phylactou, *Adv. Drug Deliv. Rev.* 44(2-3): 97-108 (2000); Phylactou *et al.*, *Hum. Mol. Genet.* 7(10): 1649-53 (1998); Rossi, *Ciba Found. Symp.* 209: 195-204 (1997); and Sigurdsson *et al.*, *Trends Biotechnol.* 13(8): 286-9 (1995), the disclosures of which are
10 incorporated herein by reference in their entireties.

Other nucleic acids useful in the therapeutic methods of the present invention are those that are capable of triplex helix formation in or near the BSG genomic locus. Such triplexing oligonucleotides are able to inhibit transcription. *See, e.g.*, Intody *et al.*, *Nucleic Acids Res.* 28(21): 4283-90 (2000); McGuffie *et al.*, *Cancer Res.* 60(14): 3790-9
15 (2000), the disclosures of which are incorporated herein by reference. Pharmaceutical compositions comprising such triplex forming oligos (TFOs) are administered in circumstances in which excessive production, or production of aberrant protein, is a pathophysiologic basis of disease.

In a preferred embodiment, the antisense molecule is derived from a nucleic acid
20 molecule encoding a BSP, preferably a BSP comprising an amino acid sequence of SEQ ID NO: 165 through 280, or a fragment, allelic variant or homolog thereof. In a more preferred embodiment, the antisense molecule is derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1 through 164, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

25 *Polypeptide Administration*

In one embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising a BSP, a fusion protein, fragment, analog or derivative thereof is administered to a subject with a clinically-significant BSP defect.

30 Protein compositions are administered, for example, to complement a deficiency in native BSP. In other embodiments, protein compositions are administered as a vaccine to elicit a humoral and/or cellular immune response to BSP. The immune response can

be used to modulate activity of BSP or, depending on the immunogen, to immunize against aberrant or aberrantly expressed forms, such as mutant or inappropriately expressed isoforms. In yet other embodiments, protein fusions having a toxic moiety are administered to ablate cells that aberrantly accumulate BSP.

5 In a preferred embodiment, the polypeptide is a BSP comprising an amino acid sequence of SEQ ID NO: 165 through 280, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the polypeptide is encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1 through 164, or a part, allelic variant, substantially similar or hybridizing nucleic acid
10 thereof.

Antibody, Agonist and Antagonist Administration

 In another embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising an antibody (including fragment or derivative thereof) of the present invention is
15 administered. As is well-known, antibody compositions are administered, for example, to antagonize activity of BSP, or to target therapeutic agents to sites of BSP presence and/or accumulation. In a preferred embodiment, the antibody specifically binds to a BSP comprising an amino acid sequence of SEQ ID NO: 165 through 280, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred
20 embodiment, the antibody specifically binds to a BSP encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1 through 164, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

 The present invention also provides methods for identifying modulators which bind to a BSP or have a modulatory effect on the expression or activity of a BSP.
25 Modulators which decrease the expression or activity of BSP (antagonists) are believed to be useful in treating breast cancer. Such screening assays are known to those of skill in the art and include, without limitation, cell-based assays and cell-free assays. Small molecules predicted via computer imaging to specifically bind to regions of a BSP can also be designed, synthesized and tested for use in the imaging and treatment of breast
30 cancer. Further, libraries of molecules can be screened for potential anticancer agents by assessing the ability of the molecule to bind to the BSPs identified herein. Molecules identified in the library as being capable of binding to a BSP are key candidates for

further evaluation for use in the treatment of breast cancer. In a preferred embodiment, these molecules will downregulate expression and/or activity of a BSP in cells.

In another embodiment of the therapeutic methods of the present invention, a pharmaceutical composition comprising a non-antibody antagonist of BSP is
5 administered. Antagonists of BSP can be produced using methods generally known in the art. In particular, purified BSP can be used to screen libraries of pharmaceutical agents, often combinatorial libraries of small molecules, to identify those that specifically bind and antagonize at least one activity of a BSP.

In other embodiments a pharmaceutical composition comprising an agonist of a
10 BSP is administered. Agonists can be identified using methods analogous to those used to identify antagonists.

In a preferred embodiment, the antagonist or agonist specifically binds to and antagonizes or agonizes, respectively, a BSP comprising an amino acid sequence of SEQ ID NO: 165 through 280, or a fusion protein, allelic variant, homolog, analog or
15 derivative thereof. In a more preferred embodiment, the antagonist or agonist specifically binds to and antagonizes or agonizes, respectively, a BSP encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1 through 164, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

Targeting Breast Tissue

20 The invention also provides a method in which a polypeptide of the invention, or an antibody thereto, is linked to a therapeutic agent such that it can be delivered to the breast or to specific cells in the breast. In a preferred embodiment, an anti-BSP antibody is linked to a therapeutic agent and is administered to a patient in need of such therapeutic agent. The therapeutic agent may be a toxin, if breast tissue needs to be
25 selectively destroyed. This would be useful for targeting and killing breast cancer cells. In another embodiment, the therapeutic agent may be a growth or differentiation factor, which would be useful for promoting breast cell function.

In another embodiment, an anti-BSP antibody may be linked to an imaging agent that can be detected using, *e.g.*, magnetic resonance imaging, CT or PET. This would be
30 useful for determining and monitoring breast function, identifying breast cancer tumors, and identifying noncancerous breast diseases.

EXAMPLES**Example 1: Gene Expression analysis**

BSGs were identified by mRNA subtraction analysis using standard methods. The sequences were extended using GeneBank sequences, Incyte's proprietary database.

- 5 From the nucleotide sequences, predicted amino acid sequences were prepared.

DEX0287_1, DEX0287_2 correspond to SEQ ID NO.1, 2 etc. DEX0131 was the parent sequence found in the mRNA subtractions.

	DEX0287_1	DEX0131_1	DEX0287_165
	DEX0287_2	flex DEX0131_1	
10	DEX0287_3	DEX0131_2	DEX0287_166
	DEX0287_4	flex DEX0131_2	
	DEX0287_5	DEX0131_3	DEX0287_167
	DEX0287_6	flex DEX0131_3	DEX0287_168
	DEX0287_7	DEX0131_4	DEX0287_169
15	DEX0287_8	flex DEX0131_4	
	DEX0287_9	DEX0131_5	
	DEX0287_10	DEX0131_6	DEX0287_170
	DEX0287_11	flex DEX0131_6	
	DEX0287_12	DEX0131_7	DEX0287_171
20	DEX0287_13	flex DEX0131_7	
	DEX0287_14	DEX0131_8	DEX0287_172
	DEX0287_15	DEX0131_9	DEX0287_173
	DEX0287_16	flex DEX0131_9	
	DEX0287_17	DEX0131_10	DEX0287_174
25	DEX0287_18	flex DEX0131_10	DEX0287_175
	DEX0287_19	DEX0131_11	DEX0287_176
	DEX0287_20	flex DEX0131_11	DEX0287_177
	DEX0287_21	DEX0131_12	DEX0287_178
	DEX0287_22	flex DEX0131_12	
30	DEX0287_23	DEX0131_13	DEX0287_179
	DEX0287_24	flex DEX0131_13	DEX0287_180
	DEX0287_25	DEX0131_14	DEX0287_181
	DEX0287_26	flex DEX0131_14	DEX0287_182
	DEX0287_27	DEX0131_15	DEX0287_183
35	DEX0287_28	flex DEX0131_15	DEX0287_184
	DEX0287_29	DEX0131_16	DEX0287_185
	DEX0287_30	DEX0131_17	DEX0287_186
	DEX0287_31	flex DEX0131_17	DEX0287_187
	DEX0287_32	DEX0131_18	DEX0287_188
40	DEX0287_33	flex DEX0131_18	DEX0287_189
	DEX0287_34	DEX0131_19	DEX0287_190
	DEX0287_35	DEX0131_20	DEX0287_191
	DEX0287_36	flex DEX0131_20	
	DEX0287_37	DEX0131_21	DEX0287_192

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	DEX0287_38	DEX0131_22 DEX0287_193
	DEX0287_39	flex DEX0131_22
	DEX0287_40	DEX0131_23 DEX0287_194
	DEX0287_41	flex DEX0131_23 DEX0287_195
5	DEX0287_42	DEX0131_24 DEX0287_196
	DEX0287_43	flex DEX0131_24
	DEX0287_44	DEX0131_25 DEX0287_197
	DEX0287_45	flex DEX0131_25 DEX0287_198
	DEX0287_46	DEX0131_26 DEX0287_199
10	DEX0287_47	flex DEX0131_26 DEX0287_200
	DEX0287_48	DEX0131_27 DEX0287_201
	DEX0287_49	flex DEX0131_27
	DEX0287_50	DEX0131_28 DEX0287_202
	DEX0287_51	flex DEX0131_28
15	DEX0287_52	DEX0131_30 DEX0287_203
	DEX0287_53	flex DEX0131_30
	DEX0287_54	DEX0131_31 DEX0287_204
	DEX0287_55	DEX0131_32 DEX0287_205
	DEX0287_56	flex DEX0131_32 DEX0287_206
20	DEX0287_57	DEX0131_33 DEX0287_207
	DEX0287_58	flex DEX0131_33
	DEX0287_59	DEX0131_34 DEX0287_208
	DEX0287_60	flex DEX0131_34
	DEX0287_61	DEX0131_35 DEX0287_209
25	DEX0287_62	flex DEX0131_35
	DEX0287_63	DEX0131_36 DEX0287_210
	DEX0287_64	DEX0131_38 DEX0287_211
	DEX0287_65	flex DEX0131_38
	DEX0287_66	DEX0131_39 DEX0287_212
30	DEX0287_67	flex DEX0131_39 DEX0287_213
	DEX0287_68	DEX0131_40 DEX0287_214
	DEX0287_69	flex DEX0131_40
	DEX0287_70	DEX0131_41 DEX0287_215
	DEX0287_71	DEX0131_42 DEX0287_216
35	DEX0287_72	DEX0131_43 DEX0287_217
	DEX0287_73	DEX0131_44 DEX0287_218
	DEX0287_74	flex DEX0131_44 DEX0287_219
	DEX0287_75	DEX0131_45 DEX0287_220
	DEX0287_76	flex DEX0131_45
40	DEX0287_77	DEX0131_46 DEX0287_221
	DEX0287_78	flex DEX0131_46
	DEX0287_79	DEX0131_47
	DEX0287_80	flex DEX0131_47
	DEX0287_81	DEX0131_48 DEX0287_222
45	DEX0287_82	flex DEX0131_48
	DEX0287_83	DEX0131_49 DEX0287_223
	DEX0287_84	flex DEX0131_49
	DEX0287_85	DEX0131_50 DEX0287_224

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	DEX0287_86	flex DEX0131_50	DEX0287_225
	DEX0287_87	DEX0131_51	DEX0287_226
	DEX0287_88	flex DEX0131_51	
	DEX0287_89	DEX0131_52	DEX0287_227
5	DEX0287_90	flex DEX0131_52	
	DEX0287_91	DEX0131_53	DEX0287_228
	DEX0287_92	flex DEX0131_53	
	DEX0287_93	DEX0131_54	DEX0287_229
	DEX0287_94	flex DEX0131_54	
10	DEX0287_95	DEX0131_55	DEX0287_230
	DEX0287_96	flex DEX0131_55	DEX0287_231
	DEX0287_97	DEX0131_56	DEX0287_232
	DEX0287_98	flex DEX0131_56	DEX0287_233
	DEX0287_99	DEX0131_58	DEX0287_234
15	DEX0287_100	flex DEX0131_58	
	DEX0287_101	DEX0131_59	DEX0287_235
	DEX0287_102	flex DEX0131_59	
	DEX0287_103	DEX0131_61	DEX0287_236
	DEX0287_104	DEX0131_62	DEX0287_237
20	DEX0287_105	flex DEX0131_62	DEX0287_238
	DEX0287_106	DEX0131_63	DEX0287_239
	DEX0287_107	flex DEX0131_63	DEX0287_240
	DEX0287_108	DEX0131_64	DEX0287_241
	DEX0287_109	DEX0131_65	DEX0287_242
25	DEX0287_110	flex DEX0131_65	
	DEX0287_111	DEX0131_66	DEX0287_243
	DEX0287_112	flex DEX0131_66	DEX0287_244
	DEX0287_113	DEX0131_68	DEX0287_245
	DEX0287_114	DEX0131_69	DEX0287_246
30	DEX0287_115	flex DEX0131_69	
	DEX0287_116	DEX0131_70	DEX0287_247
	DEX0287_117	flex DEX0131_70	
	DEX0287_118	DEX0131_71	DEX0287_248
	DEX0287_119	DEX0131_72	DEX0287_249
35	DEX0287_120	flex DEX0131_72	
	DEX0287_121	DEX0131_73	DEX0287_250
	DEX0287_122	flex DEX0131_73	
	DEX0287_123	DEX0131_74	DEX0287_251
	DEX0287_124	DEX0131_75	DEX0287_252
40	DEX0287_125	DEX0131_77	DEX0287_254
	DEX0287_126	DEX0131_78	DEX0287_255
	DEX0287_127	flex DEX0131_78	
	DEX0287_128	DEX0131_79	DEX0287_256
	DEX0287_129	flex DEX0131_79	
45	DEX0287_130	DEX0131_80	DEX0287_257
	DEX0287_131	flex DEX0131_80	
	DEX0287_132	DEX0131_81	DEX0287_258
	DEX0287_133	flex DEX0131_81	DEX0287_259

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	DEX0287_134	DEX0131_82 DEX0287_260
	DEX0287_135	flex DEX0131_82
	DEX0287_136	DEX0131_84 DEX0287_261
	DEX0287_137	flex DEX0131_84 DEX0287_262
5	DEX0287_138	DEX0131_85 DEX0287_263
	DEX0287_139	DEX0131_86 DEX0287_264
	DEX0287_140	flex DEX0131_86 DEX0287_265
	DEX0287_141	DEX0131_87 DEX0287_266
	DEX0287_142	flex DEX0131_87 DEX0287_267
10	DEX0287_143	DEX0131_88 DEX0287_268
	DEX0287_144	flex DEX0131_88
	DEX0287_145	DEX0131_89 DEX0287_269
	DEX0287_146	flex DEX0131_89
	DEX0287_147	DEX0131_90 DEX0287_270
15	DEX0287_148	flex DEX0131_90
	DEX0287_149	DEX0131_91 DEX0287_271
	DEX0287_150	DEX0131_92 DEX0287_272
	DEX0287_151	DEX0131_93 DEX0287_273
	DEX0287_152	flex DEX0131_93
20	DEX0287_153	DEX0131_94 DEX0287_274
	DEX0287_154	flex DEX0131_94
	DEX0287_155	DEX0131_95 DEX0287_275
	DEX0287_156	flex DEX0131_95
	DEX0287_157	DEX0131_96 DEX0287_276
25	DEX0287_158	flex DEX0131_96 DEX0287_277
	DEX0287_159	DEX0131_97 DEX0287_278
	DEX0287_160	flex DEX0131_97
	DEX0287_161	DEX0131_98 DEX0287_279
	DEX0287_162	flex DEX0131_98
30	DEX0287_163	DEX0131_99 DEX0287_280
	DEX0287_164	flex DEX0131_99

The expression levels from the Incyte LifeSeq database are listed below:

35	DEX0287_1	SEQ ID NO: 1	THR .0023	FTS .0038	BRN .0063	BLD .008
	DEX0287_10	SEQ ID NO: 10	CRD .0023	PAN .0035	ESO .0051	
	DEX0287_100	SEQ ID NO: 100	INL .0006			
	DEX0287_101	SEQ ID NO: 101	NOS .0073	STO .0081	ESO .0102	
	DEX0287_102	SEQ ID NO: 102	NOS .0073	STO .0081	ESO .0102	
40	DEX0287_104	SEQ ID NO: 104	LNG .0006	OVR .001	PRO .0017	BLD .0048
	DEX0287_105	SEQ ID NO: 105	LNG .0006	OVR .001	PRO .0017	BLD .0048
	DEX0287_106	SEQ ID NO: 106	PAN .0012			
	DEX0287_111	SEQ ID NO: 111	CON.0113	LIV .0189	ADR .0209	
	DEX0287_116	SEQ ID NO: 116	BLV .0016	BLV .0016	INL .0019	INL .0019
45	DEX0287_117	SEQ ID NO: 117	BLV .0016	BLV .0016	INL .0019	INL .0019

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	DEX0287_121	SEQ ID NO: 121	LMN .0083	UNC .012			
	DEX0287_122	SEQ ID NO: 122	LMN .0083	UNC .012			
	DEX0287_124	SEQ ID NO: 124	OVR .0133	ADR .0164	FAL .0189	TON .0299	
	DEX0287_126	SEQ ID NO: 126	THR .0091	UTR .0132	TON .0299		
5	DEX0287_127	SEQ ID NO: 127	THR .0091	UTR .0132	TON .0299		
	DEX0287_130	SEQ ID NO: 130	LNG .0039	ESO .0051	BON .0056	PNS .007	
	DEX0287_131	SEQ ID NO: 131	LNG .0039	ESO .0051	BON .0056	PNS .007	
	DEX0287_132	SEQ ID NO: 132	FTS .0035	CRD .0045	PNS .0187		
	DEX0287_133	SEQ ID NO: 133	FTS .0035	CRD .0045	PNS .0187		
10	DEX0287_136	SEQ ID NO: 136	UTR .0013	URE .0225			
	DEX0287_138	SEQ ID NO: 138	PNS .0023	THR .0023	MAM .0033	CRD .0068	
	DEX0287_141	SEQ ID NO: 141	PAN .0353	LMN .0416	OVR .0503	INT .1052	
	DEX0287_142	SEQ ID NO: 142	PAN .0353	LMN .0416	OVR .0503	INT .1052	
	DEX0287_15	SEQ ID NO: 15	INS .0038	ADR .006	CRD .0068		
15	DEX0287_150	SEQ ID NO: 150	BRN .0001	FTS .0001	TST .0011	MAM .0081	
	DEX0287_151	SEQ ID NO: 151	BRN .0017	UTR .0019	PAN .0035	LIV .0038	
	DEX0287_152	SEQ ID NO: 152	BRN .0017	UTR .0019	PAN .0035	LIV .0038	
	DEX0287_153	SEQ ID NO: 153	MAM .0005	ADR .0015	CON .0023		
	DEX0287_155	SEQ ID NO: 155	MAM .0033	LNG .0034	THR .0045	PNS .0047	
20	DEX0287_156	SEQ ID NO: 156	MAM .0033	LNG .0034	THR .0045	PNS .0047	
	DEX0287_157	SEQ ID NO: 157	BON .0169				
	DEX0287_16	SEQ ID NO: 16	INS .0038	ADR .006	CRD .0068		
	DEX0287_161	SEQ ID NO: 161	PRO .0102	KID .0128	NOS .022	FAL .0503	
	DEX0287_163	SEQ ID NO: 163	LIV .0057	PNS .007	GLB .0093	ADR .0149	
25	DEX0287_164	SEQ ID NO: 164	LIV .0057	PNS .007	GLB .0093	ADR .0149	
	DEX0287_17	SEQ ID NO: 17	PRO .0006				
	DEX0287_18	SEQ ID NO: 18	PRO .0006				
	DEX0287_19	SEQ ID NO: 19	BLD .0016	BMR .0064			
	DEX0287_2	SEQ ID NO: 2	THR .0023	FTS .0038	BRN .0063	BLD .008	
30	DEX0287_21	SEQ ID NO: 21	UTR .0006	PAN .0012	KID .0013		
	DEX0287_22	SEQ ID NO: 22	UTR .0006	PAN .0012	KID .0013		
	DEX0287_23	SEQ ID NO: 23	INL .0013	MAM .0024	THR .0045	LNG .0078	
	DEX0287_24	SEQ ID NO: 24	INL .0013	MAM .0024	THR .0045	LNG .0078	
	DEX0287_25	SEQ ID NO: 25	INL .0006	BON .0056			
35	DEX0287_26	SEQ ID NO: 26	PAN .0024				
	DEX0287_27	SEQ ID NO: 27	KID .0013				
	DEX0287_3	SEQ ID NO: 3	INS .001	INS .001	UTR .0013	BLV .0016	
	DEX0287_30	SEQ ID NO: 30	BRN .0078	KID .0128	ADR .0134	LNG .0134	
	DEX0287_31	SEQ ID NO: 31	BRN .0078	KID .0128	ADR .0134	LNG .0134	

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	DEX0287_33	SEQ ID NO: 33	INS .0048	PNS .007	BON .0112	URE .0225
	DEX0287_34	SEQ ID NO: 34	UTR .0013	ESO .0051	BON .0056	
	DEX0287_35	SEQ ID NO: 35	BRN .0031	THR .0045		
	DEX0287_36	SEQ ID NO: 36	BRN .0031	THR .0045		
5	DEX0287_38	SEQ ID NO: 38	PAN .0071	NOS .0073	LMN .0083	PRO .0119
	DEX0287_39	SEQ ID NO: 39	PAN .0071	NOS .0073	LMN .0083	PRO .0119
	DEX0287_4	SEQ ID NO: 4	INS .001	INS .001	UTR .0013	BLV .0016
	DEX0287_40	SEQ ID NO: 40	KID .0013	BLD .0032		
	DEX0287_42	SEQ ID NO: 42	MAM .0047			
10	DEX0287_43	SEQ ID NO: 43	MAM .0047			
	DEX0287_44	SEQ ID NO: 44	SPL .0042	MAM .0043	ESO .0051	PNS .007
	DEX0287_45	SEQ ID NO: 45	THR .0045	BRN .0048	UNC .008	ADR .0089
	DEX0287_46	SEQ ID NO: 46	URE .0225	PLE .0449		
	DEX0287_47	SEQ ID NO: 47	URE .0225	PLE .0449		
15	DEX0287_52	SEQ ID NO: 52	THY .002			
	DEX0287_53	SEQ ID NO: 53	THY .002			
	DEX0287_55	SEQ ID NO: 55	PAN .0012	LMN .0028	INS .0038	GLB .0046
	DEX0287_56	SEQ ID NO: 56	PAN .0012	LMN .0028	INS .0038	GLB .0046
	DEX0287_57	SEQ ID NO: 57	BLD .0032	NOS .0073		
20	DEX0287_58	SEQ ID NO: 58	BLD .0032	NOS .0073		
	DEX0287_59	SEQ ID NO: 59	UTR .01			
	DEX0287_60	SEQ ID NO: 60	UTR .01			
	DEX0287_61	SEQ ID NO: 61	INS .001	KID .0013	BLD .0032	INL .0032
	DEX0287_62	SEQ ID NO: 62	INS .001	KID .0013	BLD .0032	INL .0032
25	DEX0287_64	SEQ ID NO: 64	SAG .0593	TON .0896	CTL .1252	PAN .1422
	DEX0287_65	SEQ ID NO: 65	SAG .0593	TON .0896	CTL .1252	PAN .1422
	DEX0287_66	SEQ ID NO: 66	INL .0013	MAM .0024	THR .0045	LNG .0078
	DEX0287_67	SEQ ID NO: 67	INL .0013	MAM .0024	THR .0045	LNG .0078
	DEX0287_7	SEQ ID NO: 7	UTR .0075	PLE .0449		
30	DEX0287_73	SEQ ID NO: 73	THR .0045	PAN .0059	OVR .0123	MAM .0255
	DEX0287_75	SEQ ID NO: 75	PNS .0117	UTR .0176	LMN .0222	
	DEX0287_77	SEQ ID NO: 77	BRN .0004	KID .0006	ADR .0013	ADR .0015
	DEX0287_78	SEQ ID NO: 78	BRN .0004	KID .0006	ADR .0013	ADR .0015
	DEX0287_85	SEQ ID NO: 85	INS .0019	TON .0299		
35	DEX0287_90	SEQ ID NO: 90	BRN .0002	BRN .0006	KID .0006	LNG .0006
	DEX0287_91	SEQ ID NO: 91	LNG .0017			
	DEX0287_92	SEQ ID NO: 92	LNG .0017			
	DEX0287_93	SEQ ID NO: 93	LNG .0335			
	DEX0287_94	SEQ ID NO: 94	LNG .0335			

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DEX0287_95 SEQ ID NO: 95 SKN .0015 BLD .0016 TNS .0016 SPL .002
 DEX0287_97 SEQ ID NO: 97 BRN .0006 MAM .0009 UTR .0013 INL .0013
 DEX0287_99 SEQ ID NO: 99 INL .0006

Abbreviation for tissues:

- 5 BLO Blood; BRN Brain; CON Connective Tissue; CRD Heart; FTS Fetus; INL Intestine, Large; INS Intestine, Small; KID Kidney; LIV Liver; LNG Lung; MAM Breast; MSL Muscles; NRV Nervous Tissue; OVR Ovary; PRO Prostate; STO Stomach; THR Thyroid Gland; TNS Tonsil / Adenoids; UTR Uterus

10 **Example 2: Relative Quantitation of Gene Expression**

- Real-Time quantitative PCR with fluorescent Taqman probes is a quantitation detection system utilizing the 5'-3' nuclease activity of Taq DNA polymerase. The method uses an internal fluorescent oligonucleotide probe (Taqman) labeled with a 5' reporter dye and a downstream, 3' quencher dye. During PCR, the 5'-3' nuclease activity of Taq DNA polymerase releases the reporter, whose fluorescence can then be detected by the laser detector of the Model 7700 Sequence Detection System (PE Applied Biosystems, Foster City, CA, USA). Amplification of an endogenous control is used to standardize the amount of sample RNA added to the reaction and normalize for Reverse Transcriptase (RT) efficiency. Either cyclophilin, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), ATPase, or 18S ribosomal RNA (rRNA) is used as this endogenous control. To calculate relative quantitation between all the samples studied, the target RNA levels for one sample were used as the basis for comparative results (calibrator). Quantitation relative to the "calibrator" can be obtained using the standard curve method or the comparative method (User Bulletin #2: ABI PRISM 7700 Sequence Detection System).

- The tissue distribution and the level of the target gene are evaluated for every sample in normal and cancer tissues. Total RNA is extracted from normal tissues, cancer tissues, and from cancers and the corresponding matched adjacent tissues. Subsequently, first strand cDNA is prepared with reverse transcriptase and the polymerase chain reaction is done using primers and Taqman probes specific to each target gene. The results are analyzed using the ABI PRISM 7700 Sequence Detector. The absolute numbers are relative levels of expression of the target gene in a particular tissue compared to the calibrator tissue.

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One of ordinary skill can design appropriate primers. The relative levels of expression of the BSNA versus normal tissues and other cancer tissues can then be determined. All the values are compared to a normal tissue (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

The relative levels of expression of the BSNA in pairs of matching samples and 1 cancer and 1 normal/normal adjacent of tissue may also be determined. All the values are compared to a normal tissue (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

In the analysis of matching samples, BSNAs show a high degree of tissue specificity for the tissue of interest. These results confirm the tissue specificity results obtained with normal pooled samples.

Further, the level of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual are compared. This comparison provides an indication of specificity for the cancer stage (*e.g.* higher levels of mRNA expression in the cancer sample compared to the normal adjacent).

Altogether, the high level of tissue specificity, plus the mRNA overexpression in matching samples tested are indicative of SEQ ID NO: 1 through 81 being diagnostic markers for cancer.

DEX0131_24 (sqmam047); DEX0289_43 (SEQ ID NO: 43)

Semi-quantitative PCR was done using the following primers:

Primer	DexSeqID	From	To	Primer Length
sqmam047F	DEX0289_43	172	193	22
sqmam047R	DEX0289_43	413	390	24

Table 1. The absolute numbers are relative levels of expression of sqmam047 in 12 normal samples from 12 different tissues. These RNA samples are from single individual or are commercially available pools, originated by pooling samples of a particular tissue from different individuals.. Using Polymerase Chain Reaction (PCR) technology expression levels were analyzed from four 10x serial cDNA dilutions in duplicate. Relative expression levels of 0, 1, 10, 100 and 1000 are used to evaluate gene

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expression. A positive reaction in the most dilute sample indicates the highest relative expression value.

TISSUE	NORMAL
Breast	100
Colon	10
Endometrium	100
Kidney	1000
Liver	10
Lung	10
Ovary	100
Prostate	10
Small Intestine	10
Stomach	1
Testis	1000
Uterus	1

- 5 Relative levels of expression in Table 1 show that all the normal tissues have a different degree of expression with normal kidney and testis having the highest expression of sqmam047.

- 10 **Table 2.** The absolute numbers are relative levels of expression of sqmam047 in 12 cancer samples from 12 different tissues. Using Polymerase Chain Reaction (PCR) technology expression levels were analyzed from four 10x serial cDNA dilutions in duplicate. Relative expression levels of 0, 1, 10, 100 and 1000 are used to evaluate gene expression. A positive reaction in the most dilute sample indicates the highest relative expression value.

TISSUE	CANCER
Bladder	10
Breast	10
Colon	1000
Kidney	100
Liver	100
Lung	100
Ovary	100
Pancreas	10
Prostate	100
Stomach	1000
Testes	100
Uterus	100

Relative levels of expression in Table 2 show that sqmam047 is expressed in most of the carcinomas tested.

Table 3. The absolute numbers are relative levels of expression of sqmam047 in 6 mammary gland cancer matching samples. A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

Using Polymerase Chain Reaction (PCR) technology expression levels were analyzed from four 10x serial cDNA dilutions in duplicate. Relative expression levels of 0, 1, 10, 100 and 1000 are used to evaluate gene expression. A positive reaction in the most dilute sample indicates the highest relative expression value.

SAMPLE ID	TISSUE	CANCER	NORMAL ADJACENT TISSUE
S99522A/B	mammary gland 1	1000	1
4005724A2/B3	mammary gland 2	100	10
4005599A4/B2	mammary gland 3	1000	1
4005629A2/B2	mammary gland 4	10	1000
S9822245A/B	mammary gland 5	1000	100
S9819997A/B	mammary gland 6	1000	100

Relative levels of expression in Table 2 shows that sqmam047 is expressed in all six mammary gland cancer samples and matching normal adjacent tissue (NAT). This assay shows that sqmam047 is upregulated in 5 out of 6 (83%) of the matching samples analyzed.

Experiments are underway to design and test primers and probe for quantitative PCR.

The chromosomal locations were determined for several of the sequences. Specifically:

- DEX0287_2 chromosome 1
- DEX0287_6 chromosome 8
- DEX0287_8 chromosome 2
- DEX0287_11 chromosome 1
- DEX0287_12 chromosome 9
- DEX0287_13 chromosome 9
- DEX0287_17 chromosome 12
- DEX0287_18 chromosome 12
- DEX0287_20 chromosome 3
- DEX0287_24 chromosome 1
- DEX0287_26 chromosome 11
- DEX0287_28 chromosome 19
- DEX0287_30 chromosome 16
- DEX0287_38 chromosome 7
- DEX0287_39 chromosome 7

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	DEX0287_41	chromosome 19
	DEX0287_44	chromosome 8
	DEX0287_45	chromosome 4
	DEX0287_47	chromosome 3
5	DEX0287_48	chromosome 2
	DEX0287_51	chromosome 1
	DEX0287_52	chromosome 8
	DEX0287_53	chromosome 8
	DEX0287_54	chromosome 8
10	DEX0287_56	chromosome 5
	DEX0287_58	chromosome 7
	DEX0287_62	chromosome 8
	DEX0287_63	chromosome 3
	DEX0287_65	chromosome 4
15	DEX0287_68	chromosome 10
	DEX0287_69	chromosome 13
	DEX0287_70	chromosome 8
	DEX0287_71	chromosome 9
	DEX0287_72	chromosome 6
20	DEX0287_74	chromosome 16
	DEX0287_77	chromosome Un
	DEX0287_78	chromosome Un
	DEX0287_80	chromosome 2
	DEX0287_82	chromosome 3
25	DEX0287_86	chromosome 16
	DEX0287_88	chromosome 2
	DEX0287_89	chromosome 8
	DEX0287_90	chromosome 8
	DEX0287_94	chromosome 16
30	DEX0287_103	chromosome 16
	DEX0287_107	chromosome 18
	DEX0287_108	chromosome 8
	DEX0287_109	chromosome 4
	DEX0287_110	chromosome 4
35	DEX0287_112	chromosome 2
	DEX0287_114	chromosome 6
	DEX0287_115	chromosome 6
	DEX0287_116	chromosome 11
	DEX0287_117	chromosome 12
40	DEX0287_119	chromosome Un
	DEX0287_122	chromosome 1
	DEX0287_123	chromosome 17
	DEX0287_124	chromosome 8
	DEX0287_131	chromosome 5
45	DEX0287_132	chromosome 5
	DEX0287_133	chromosome 5
	DEX0287_137	chromosome 15
	DEX0287_139	chromosome 2

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	DEX0287_140	chromosome 2
	DEX0287_149	chromosome 6
	DEX0287_151	chromosome 7
	DEX0287_152	chromosome 7
5	DEX0287_153	chromosome 8
	DEX0287_154	chromosome 8
	DEX0287_156	chromosome 1
	DEX0287_157	chromosome 10
10	DEX0287_158	chromosome 10

Example 3: Protein Expression

The BSNA is amplified by polymerase chain reaction (PCR) and the amplified DNA fragment encoding the BSNA is subcloned in pET-21d for expression in *E. coli*. In addition to the BSNA coding sequence, codons for two amino acids, Met-Ala, flanking the NH₂-terminus of the coding sequence of BSNA, and six histidines, flanking the COOH-terminus of the coding sequence of BSNA, are incorporated to serve as initiating Met/restriction site and purification tag, respectively.

An over-expressed protein band of the appropriate molecular weight may be observed on a Coomassie blue stained polyacrylamide gel. This protein band is confirmed by Western blot analysis using monoclonal antibody against 6X Histidine tag.

Large-scale purification of BSP was achieved using cell paste generated from 6-liter bacterial cultures, and purified using immobilized metal affinity chromatography (IMAC). Soluble fractions that had been separated from total cell lysate were incubated with a nickle chelating resin. The column was packed and washed with five column volumes of wash buffer. BSP was eluted stepwise with various concentration imidazole buffers.

Example 4: Protein Fusions

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector. For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in

Example 2, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced. If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the
5 vector can be modified to include a heterologous signal sequence. *See, e. g.*, WO 96/34891.

Example 5: Production of an Antibody from a Polypeptide

In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such
10 cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100, µg/ml of streptomycin. The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any
15 suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP20), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands *et al.*, *Gastroenterology* 80: 225-232 (1981).

20 The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide. Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to
25 obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such
30 antibodies comprise anti-idiotypic antibodies to the protein specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies. Using the Jameson-Wolf methods the following epitopes were predicted. (Jameson and

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Wolf, CABIOS, 4(1), 181-186, 1988, the contents of which are incorporated by reference).

The predicted antigenicity for the amino acid sequences is as follows:

5	DEX0287_165 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
	14-33	1.17	20
	DEX0287_166 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
	5-22	1.08	18
10	DEX0287_167 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
	6-15	1.06	10
	DEX0287_168 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
15	177-188	1.06	12
	88-107	1.03	20
	DEX0287_169 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
	2-12	1.05	11
20	DEX0287_171 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
	12-25	1.06	14
	49-67	1.02	19
	DEX0287_173 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
25	9-29	1.37	21
	DEX0287_176 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
	34-47	1.11	14
30	DEX0287_177 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
	191-202	1.19	12
	113-149	1.05	37
	246-259	1.04	14
35	DEX0287_179 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
	63-84	1.22	22
	30-39	1.08	10
	DEX0287_180 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
40	60-81	1.23	22
	27-36	1.08	10
	DEX0287_182 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
45	710-723	1.17	14
	150-166	1.11	17
	320-335	1.09	16
	40-55	1.04	16
	177-237	1.01	61
50	DEX0287_184 Antigenicity Index (Jameson-Wolf)		
	positions	AI avg	length
	1405-1417	1.14	13
	717-779	1.13	63
	794-824	1.11	31
55	1141-1157	1.10	17
	839-874	1.09	36

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	1419-1433	1.05	15
	1278-1287	1.03	10
	1036-1052	1.02	17
	1292-1327	1.01	36
5	1480-1503	1.01	24
	1230-1255	1.01	26
	1000-1030	1.00	31
	DEX0287_189 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
10	389-398	1.26	10
	349-382	1.22	34
	59-73	1.20	15
	DEX0287_194 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
15	43-63	1.24	21
	DEX0287_195 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
	75-85	1.04	11
	42-51	1.03	10
20	DEX0287_197 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
	41-57	1.07	17
	DEX0287_198 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
25	814-826	1.25	13
	736-753	1.15	18
	462-471	1.15	10
	649-690	1.14	42
	781-807	1.11	27
30	633-643	1.09	11
	124-138	1.08	15
	861-872	1.05	12
	52-87	1.04	36
	395-405	1.03	11
35	91-118	1.03	28
	DEX0287_200 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
	158-189	1.12	32
	259-272	1.06	14
40	61-100	1.00	40
	DEX0287_205 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
	63-72	1.16	10
	DEX0287_206 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
45	90-101	1.08	12
	DEX0287_207 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
	22-34	1.27	13
50	DEX0287_209 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
	17-55	1.02	39
	DEX0287_212 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
55	19-32	1.10	14
	DEX0287_213 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
	51-72	1.23	22
	18-27	1.08	10

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	DEX0287_214	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	28-38	1.12 11
5	DEX0287_218	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	2-25	1.18 24
	DEX0287_219	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
10	502-511	1.36 10
	546-587	1.15 42
	153-191	1.05 39
	193-213	1.03 21
	DEX0287_223	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
15	18-33	1.14 16
	DEX0287_226	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	11-21	1.07 11
20	DEX0287_227	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	39-66	1.17 28
	DEX0287_230	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	68-78	1.00 11
25	DEX0287_231	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	153-190	1.16 38
	205-231	1.06 27
	21-37	1.00 17
30	DEX0287_232	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	30-41	1.02 12
	DEX0287_233	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
35	239-249	1.13 11
	DEX0287_234	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	35-46	1.25 12
40	DEX0287_238	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	91-100	1.19 10
	140-150	1.04 11
	DEX0287_244	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
45	662-694	1.20 33
	36-61	1.12 26
	98-118	1.10 21
	283-334	1.02 52
	699-740	1.01 42
50	DEX0287_245	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	7-16	1.09 10
	DEX0287_251	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
55	2-61	1.05 60
	DEX0287_262	Antigenicity Index(Jameson-Wolf)
	positions	AI avg length
	51-98	1.28 48
	154-164	1.13 11

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	236-265	1.08	30
	179-220	1.08	42
	334-363	1.04	30
	290-312	1.02	23
5	DEX0287_263 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
	4-24	1.03	21
	DEX0287_265 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
10	8-17	1.05	10
	DEX0287_273 Antigenicity Index(Jameson-Wolf)		
	positions	AI avg	length
	7-22	1.11	16
	DEX0287_279 Antigenicity Index(Jameson-Wolf)		
15	positions	AI avg	length
	10-21	1.15	12

The predicted helicity for the amino acid sequences is listed below:

	DEX0287_166	PredHel=1	Topology=i21-41o
20	DEX0287_171	PredHel=1	Topology=o26-48i
	DEX0287_174	PredHel=1	Topology=o22-44i
	DEX0287_176	PredHel=1	Topology=o15-32i
	DEX0287_179	PredHel=1	Topology=o40-62i
	DEX0287_180	PredHel=1	Topology=o37-59i
25	DEX0287_181	PredHel=1	Topology=i12-34o
	DEX0287_183	PredHel=1	Topology=o10-32i
	DEX0287_186	PredHel=2	Topology=i34-56o60-82i
	DEX0287_187	PredHel=3	Topology=o20-39i46-68o73-92i
	DEX0287_189	PredHel=1	Topology=i200-222o
30	DEX0287_190	PredHel=1	Topology=o20-42i
	DEX0287_191	PredHel=1	Topology=o10-32i
	DEX0287_202	PredHel=2	Topology=i5-27o67-89i
	DEX0287_203	PredHel=1	Topology=o65-87i
	DEX0287_208	PredHel=1	Topology=o15-37i
35	DEX0287_209	PredHel=1	Topology=o51-73i
	DEX0287_213	PredHel=1	Topology=o28-50i
	DEX0287_217	PredHel=1	Topology=o22-44i
	DEX0287_222	PredHel=1	Topology=i7-24o
	DEX0287_224	PredHel=1	Topology=o15-37i
40	DEX0287_227	PredHel=2	Topology=i2-21o68-85i
	DEX0287_234	PredHel=1	Topology=i48-70o
	DEX0287_235	PredHel=1	Topology=i20-42o
	DEX0287_236	PredHel=1	Topology=o10-32i
	DEX0287_244	PredHel=1	Topology=o616-638i
45	DEX0287_248	PredHel=1	Topology=i7-26o
	DEX0287_252	PredHel=2	Topology=i5-27o42-64i
	DEX0287_258	PredHel=1	Topology=o37-59i
	DEX0287_260	PredHel=1	Topology=o15-32i
	DEX0287_263	PredHel=1	Topology=i23-45o
50	DEX0287_265	PredHel=3	Topology=o15-37i74-96o169-191i

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DEX0287_271	PredHel=3	Topology=i5-22o32-54i61-83o
DEX0287_274	PredHel=1	Topology=o62-84i
DEX0287_280	PredHel=2	Topology=i7-29o33-55i

- 5 Examples of post-translational modifications (PTMs) of the BSPs of this invention are listed below. In addition, antibodies that specifically bind such post-translational modifications may be useful as a diagnostic or as therapeutic. Using the ProSite database (Bairoch et al., Nucleic Acids Res. 25(1):217-221 (1997), the contents of which are incorporated by reference), the following PTMs were predicted for the LSPs
- 10 of the invention (http://npsa-pbil.ibcp.fr/cgi-bin/npsa_automat.pl?page=npsa_prosite.html most recently accessed October 23, 2001). For full definitions of the PTMs see <http://www.expasy.org/cgi-bin/prosite-list.pl> most recently accessed October 23, 2001.
- DEX0287_165 Ck2_Phospho_Site 50-53;73-76; Myristyl 46-51; Pkc_Phospho_Site 13-15;73-75; Tyr_Phospho_Site 14-21;15-21;
- 15 DEX0287_166 Ck2_Phospho_Site 43-46; Pkc_Phospho_Site 6-8;17-19;
- DEX0287_167 Pkc_Phospho_Site 42-44; Tyr_Phospho_Site 28-34;
- DEX0287_168 Atp_Gtp_A 40-47; Ck2_Phospho_Site 7-10;127-130; Myristyl 17-22; Pkc_Phospho_Site 50-52;178-180;201-203;
- DEX0287_169 Myristyl 26-31;47-52;51-56;
- 20 DEX0287_170 Asn_Glycosylation 31-34; Ck2_Phospho_Site 10-13;
- DEX0287_171 Myristyl 9-14; Pkc_Phospho_Site 13-15;14-16;
- DEX0287_172 Pkc_Phospho_Site 29-31;
- DEX0287_173 Asn_Glycosylation 23-26;
- DEX0287_174 Prokar_Lipoprotein 23-33;
- 25 DEX0287_175 Camp_Phospho_Site 3-6; Myristyl 31-36;90-95;
- DEX0287_176 Asn_Glycosylation 44-47;
- DEX0287_177 Asn_Glycosylation 55-58; Ck2_Phospho_Site 91-94;193-196; Myristyl 141-146;199-204;200-205;223-228; Pkc_Phospho_Site 26-28;34-36;91-93;95-97;115-117;121-123;252-254;253-255;
- 30 DEX0287_178 Ck2_Phospho_Site 43-46;
- DEX0287_179 Asn_Glycosylation 4-7; Myristyl 2-7;3-8;16-21;47-52; Pkc_Phospho_Site 7-9;12-14;64-66;
- DEX0287_180 Myristyl 13-18;44-49; Pkc_Phospho_Site 4-6;9-11;61-63;96-98;
- DEX0287_181 Asn_Glycosylation 37-40; Pkc_Phospho_Site 49-51;54-56;
- 35 DEX0287_182 Asn_Glycosylation 7-10;70-73;336-339;408-411;519-522; Camp_Phospho_Site 561-564; Ck2_Phospho_Site 65-68;176-179;181-184;186-189;191-194;200-203;201-204;217-220;229-232;231-234;247-250;317-320;321-324;322-325;359-362;365-

- 368;410-413;416-419;457-460;484-487;510-513;521-524;569-572;627-630;631-634;636-639;661-664;718-721; Cpsase_2 618-625; Myristyl 130-135;291-296;332-337;458-463;604-609;680-685; Pkc_Phospho_Site 44-46;150-152;181-183;214-216;397-399;450-452;713-715; Tyr_Phospho_Site 578-585; Uch_2_2 281-298;
- 5 DEX0287_183 Amidation 22-25;
- DEX0287_184 Asn_Glycosylation 61-64;154-157;241-244;345-348; Camp_Phospho_Site 3-6; Ck2_Phospho_Site 56-59;621-624;839-842;851-854; Myristyl 32-37;37-42;38-43;39-44;40-45;41-46;42-47;89-94;94-99;96-101;165-170;169-174;172-177;173-178;257-262;258-263;267-272;271-276;324-329;444-449;456-461;484-489;513-518;629-634;926-931;952-957; Pkc_Phospho_Site 316-318;844-846;
- 10 DEX0287_185 Pkc_Phospho_Site 20-22;
- DEX0287_186 Asn_Glycosylation 10-13;75-78; Myristyl 28-33; Pkc_Phospho_Site 82-84; Prokar_Lipoprotein 8-18;19-29;
- DEX0287_187 Asn_Glycosylation 19-22;84-87; Myristyl 37-42; Pkc_Phospho_Site 91-93;
- 15 DEX0287_188 Asn_Glycosylation 42-45; Pkc_Phospho_Site 13-15; Tyr_Phospho_Site 30-36;
- DEX0287_189 Asn_Glycosylation 52-55;131-134;145-148;343-346; Camp_Phospho_Site 240-243; Ck2_Phospho_Site 57-60;68-71;119-122;363-366; Myristyl 102-107;178-183;231-236;353-358; Pkc_Phospho_Site 61-63;68-70;119-121;238-240;243-245;254-256;374-376;
- 20 DEX0287_190 Amidation 6-9;
- DEX0287_192 Asn_Glycosylation 34-37; Ck2_Phospho_Site 15-18;27-30;
- DEX0287_193 Myristyl 42-47;72-77;76-81; Pkc_Phospho_Site 53-55;
- DEX0287_194 Ck2_Phospho_Site 57-60; Myristyl 55-60;72-77;
- 25 DEX0287_195 Camp_Phospho_Site 36-39; Ck2_Phospho_Site 75-78;
- DEX0287_197 Asn_Glycosylation 20-23; Camp_Phospho_Site 26-29; Ck2_Phospho_Site 38-41;43-46; Myristyl 16-21;63-68;
- DEX0287_198 Amidation 653-656; Asn_Glycosylation 75-78;673-676; Camp_Phospho_Site 126-129; Ck2_Phospho_Site 13-16;66-69;76-79;77-80;97-100;99-102;129-132;225-228;400-403;434-437;461-464;481-484;547-550;603-606;610-613;801-804;814-817;818-821;834-837;865-868;917-920;919-922; Glycosaminoglycan 854-857; Myristyl 72-77;155-160;173-178;326-331;440-445;507-512;508-513;576-581;639-644;740-745;741-746;744-749;806-811;855-860; Pkc_Phospho_Site 31-33;61-63;66-68;163-165;177-179;400-402;441-443;465-467;466-468;495-497;586-588;648-650;801-803;904-906;
- 30 DEX0287_199 Ck2_Phospho_Site 7-10; Pkc_Phospho_Site 13-15;
- DEX0287_200 Amidation 44-47;93-96; Asn_Glycosylation 172-175; Camp_Phospho_Site 108-111;158-161; Ck2_Phospho_Site 33-36;260-263;290-293; Glycosaminoglycan 78-81; Myristyl 10-15;73-78;100-105;112-117;177-182;227-232;288-293; Pkc_Phospho_Site 126-128;164-166;245-247;260-262;

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- DEX0287_201 Asn_Glycosylation 82-85; Ck2_Phospho_Site 58-61;91-94; Myristyl 8-13;16-21;23-28;55-60; Pkc_Phospho_Site 28-30;75-77;79-81;96-98;
- DEX0287_202 Ck2_Phospho_Site 26-29;47-50;
- DEX0287_203 Ck2_Phospho_Site 17-20; Myristyl 55-60; Pkc_Phospho_Site 59-61;
- 5 DEX0287_204 Ck2_Phospho_Site 21-24;35-38; Myristyl 8-13; Pkc_Phospho_Site 12-14;
- DEX0287_205 Pkc_Phospho_Site 16-18;75-77;
- DEX0287_206 Ck2_Phospho_Site 90-93; Myristyl 21-26;58-63;
- DEX0287_207 Asn_Glycosylation 22-25;41-44;45-48; Myristyl 23-28; Pkc_Phospho_Site 50-52;
- DEX0287_210 Pkc_Phospho_Site 22-24;
- 10 DEX0287_211 Ck2_Phospho_Site 36-39; Myristyl 2-7;94-99;
- DEX0287_212 Asn_Glycosylation 17-20;42-45; Ck2_Phospho_Site 20-23; Myristyl 21-26;
- Pkc_Phospho_Site 12-14;29-31;
- DEX0287_213 Asn_Glycosylation 101-104; Myristyl 4-9;35-40; Pkc_Phospho_Site 52-54;87-89;
- DEX0287_214 Pkc_Phospho_Site 31-33;34-36;
- 15 DEX0287_215 Asn_Glycosylation 47-50; Pkc_Phospho_Site 28-30;38-40; Tyr_Phospho_Site 29-36;30-36;
- DEX0287_216 Camp_Phospho_Site 40-43;59-62; Ck2_Phospho_Site 17-20;48-51;106-109;
- Pkc_Phospho_Site 28-30;29-31;45-47;53-55;124-126;
- DEX0287_218 Amidation 109-112; Asn_Glycosylation 59-62; Camp_Phospho_Site 68-71; Myristyl 19-24;83-88; Pkc_Phospho_Site 58-60;76-78;92-94;
- 20 DEX0287_219 Amidation 523-526; Asn_Glycosylation 60-63;395-398;455-458; Camp_Phospho_Site 44-47;346-349;507-510;549-552; Ck2_Phospho_Site 11-14;48-51;165-168;191-194;216-219;226-229;231-234;256-259;313-316;314-317;349-352;356-359;376-379;397-400;401-404;402-405;403-406;444-447;457-460;458-461;463-466;472-475;484-487;
- 25 Myristyl 85-90;243-248;250-255;288-293;369-374; Pkc_Phospho_Site 47-49;48-50;77-79;88-90;134-136;184-186;233-235;282-284;318-320;329-331;438-440;499-501;503-505;554-556;576-578;
- DEX0287_220 Myristyl 36-41; Pkc_Phospho_Site 5-7;40-42; Tyr_Phospho_Site 26-32;
- DEX0287_223 Myristyl 24-29;
- 30 DEX0287_225 Asn_Glycosylation 297-300; Camp_Phospho_Site 266-269; Ck2_Phospho_Site 37-40;77-80;107-110; Myristyl 8-13;53-58;57-62;125-130;177-182; Pkc_Phospho_Site 12-14;93-95;107-109;250-252;265-267;299-301;308-310; Prokar_Lipoprotein 177-187;
- Thiol_Protease_His 255-265;
- DEX0287_226 Pkc_Phospho_Site 4-6;12-14;
- 35 DEX0287_227 Amidation 30-33; Pkc_Phospho_Site 65-67; Prokar_Lipoprotein 2-12;
- DEX0287_228 Pkc_Phospho_Site 18-20;
- DEX0287_229 Asn_Glycosylation 37-40; Ck2_Phospho_Site 10-13; Myristyl 3-8; Pkc_Phospho_Site 36-38;
- DEX0287_230 Camp_Phospho_Site 45-48; Ck2_Phospho_Site 9-12;

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- DEX0287_231 Amidation 25-28; Camp_Phospho_Site 156-159; Glycosaminoglycan 15-18; Myristyl 11-16;12-17;18-23;22-27;38-43;78-83;82-87;83-88;90-95;101-106;111-116;115-120;123-128;166-171;231-236;232-237;246-251;263-268; Pkc_Phospho_Site 93-95;251-253; Prokar_Lipoprotein 7-17;
- 5 DEX0287_232 Asn_Glycosylation 86-89; Ck2_Phospho_Site 21-24; Myristyl 96-101; Pkc_Phospho_Site 18-20;
- DEX0287_233 Amidation 72-75; Asn_Glycosylation 119-122;120-123; Camp_Phospho_Site 107-110;216-219; Ck2_Phospho_Site 28-31;43-46;63-66;160-163;169-172;187-190; Myristyl 69-74;158-163; Pkc_Phospho_Site 17-19;24-26;35-37;52-54;59-61;106-108;122-124;184-186; Prokar_Lipoprotein 248-258;
- 10 DEX0287_234 Asn_Glycosylation 43-46; Myristyl 56-61;
- DEX0287_236 Leucine_Zipper 12-33;
- DEX0287_237 Camp_Phospho_Site 6-9; Myristyl 54-59;
- DEX0287_238 Ck2_Phospho_Site 66-69;96-99; Glycosaminoglycan 50-53; Myristyl 47-52;49-54;53-58;62-67;111-116;112-117; Pkc_Phospho_Site 12-14;131-133;191-193;209-211;
- 15 DEX0287_239 Asn_Glycosylation 2-5; Ck2_Phospho_Site 54-57; Pkc_Phospho_Site 54-56;
- DEX0287_240 Amidation 53-56; Asn_Glycosylation 107-110; Camp_Phospho_Site 32-35;60-63; Pkc_Phospho_Site 4-6;35-37;63-65;70-72;71-73;84-86;123-125;
- DEX0287_241 Asn_Glycosylation 37-40; Camp_Phospho_Site 14-17; Ck2_Phospho_Site 7-10;
- 20 Pkc_Phospho_Site 13-15;
- DEX0287_242 Ck2_Phospho_Site 18-21; Myristyl 12-17;
- DEX0287_243 Pkc_Phospho_Site 30-32;
- DEX0287_244 Asn_Glycosylation 72-75;261-264;370-373;474-477;516-519; Camp_Phospho_Site 224-227;366-369; Ck2_Phospho_Site 36-39;180-183;253-256;333-336;380-383;457-460;778-781; Myristyl 177-182;217-222;266-271;319-324;368-373;381-386;384-389;393-398;482-487;575-580;585-590;649-654;731-736;732-737; Pkc_Phospho_Site 50-52;151-153;315-317;475-477;507-509;513-515;637-639;653-655;694-696; Tyr_Phospho_Site 193-200;290-296;681-688;
- 25 DEX0287_245 Ck2_Phospho_Site 9-12;27-30;29-32; Myristyl 16-21; Pkc_Phospho_Site 5-7;21-23;24-26;
- 30 DEX0287_246 Glycosaminoglycan 25-28; Myristyl 24-29;
- DEX0287_248 Asn_Glycosylation 34-37; Ck2_Phospho_Site 36-39;
- DEX0287_249 Asn_Glycosylation 43-46;51-54; Ck2_Phospho_Site 34-37; Pkc_Phospho_Site 70-72;
- DEX0287_250 Asn_Glycosylation 35-38; Ck2_Phospho_Site 37-40; Myristyl 3-8; Pkc_Phospho_Site 57-59;
- 35 DEX0287_251 Amidation 28-31;75-78;101-104; Camp_Phospho_Site 7-10; Ck2_Phospho_Site 19-22;48-51;111-114; Myristyl 16-21;83-88;84-89;96-101; Pkc_Phospho_Site 3-5;10-12;26-28;
- DEX0287_252 Myristyl 33-38;52-57;

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- DEX0287_253 Pkc_Phospho_Site 16-18;
- DEX0287_254 Myristyl 14-19; Prokar_Lipoprotein 8-18;
- DEX0287_255 Asn_Glycosylation 42-45; Camp_Phospho_Site 12-15; Myristyl 4-9;
- DEX0287_256 Asn_Glycosylation 8-11;
- 5 DEX0287_257 Pkc_Phospho_Site 11-13;
- DEX0287_258 Pkc_Phospho_Site 23-25;
- DEX0287_259 Myristyl 19-24; Pkc_Phospho_Site 12-14;
- DEX0287_260 Amidation 10-13; Myristyl 18-23;
- DEX0287_262 Asn_Glycosylation 53-56;76-79; Camp_Phospho_Site 64-67; Ck2_Phospho_Site 179-
 10 182;190-193;216-219;253-256;338-341; Dnaj_1 168-187; Glycosaminoglycan 67-70;83-
 86;85-88;300-303; Myristyl 54-59;84-89;99-104;163-168;172-177;227-232;232-
 237;301-306; N6_Mtase 288-294; Pkc_Phospho_Site 42-44;122-124;305-307; Rgd 261-
 263; Tyr_Phospho_Site 337-343;
- DEX0287_263 Camp_Phospho_Site 47-50; Myristyl 4-9; Pkc_Phospho_Site 8-10;19-21;
- 15 DEX0287_264 Ck2_Phospho_Site 7-10; Myristyl 3-8; Pkc_Phospho_Site 17-19;
- DEX0287_265 Ck2_Phospho_Site 10-13;144-147; Myristyl 17-22;157-162; Pkc_Phospho_Site 114-
 116;199-201; Prokar_Lipoprotein 15-25;
- DEX0287_266 Pkc_Phospho_Site 3-5;8-10;
- DEX0287_267 Ck2_Phospho_Site 58-61;80-83;84-87; Pkc_Phospho_Site 28-30;
- 20 DEX0287_271 Myristyl 27-32;141-146;144-149; Pkc_Phospho_Site 17-19;55-57;90-92;111-113;
- DEX0287_272 Myristyl 3-8;
- DEX0287_273 Asn_Glycosylation 82-85; Ck2_Phospho_Site 63-66; Myristyl 9-14;79-84;
- DEX0287_274 Asn_Glycosylation 30-33; Pkc_Phospho_Site 31-33;
- DEX0287_276 Asn_Glycosylation 11-14;12-15;
- 25 DEX0287_277 Myristyl 4-9;41-46; Pkc_Phospho_Site 15-17;21-23;68-70;
- DEX0287_278 Asn_Glycosylation 12-15; Tyr_Phospho_Site 29-36;
- DEX0287_279 Myristyl 12-17; Pkc_Phospho_Site 32-34;

30 **Example 6: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

RNA is isolated from individual patients or from a family of individuals that have a phenotype of interest. cDNA is then generated from these RNA samples using protocols known in the art. *See*, Sambrook (2001), *supra*. The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO: 1
 35 through 164. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions

described in Sidransky *et al.*, *Science* 252(5006): 706-9 (1991). *See also* Sidransky *et al.*, *Science* 278(5340): 1054-9 (1997).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies).

5 The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing. PCR products is cloned into T-tailed vectors as described in Holton *et al.*, *Nucleic Acids Res.*, 19: 1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected
10 individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements may also be determined. Genomic clones are nick-translated with digoxigenin deoxyuridine 5' triphosphate (Boehringer Mannheim), and FISH is performed as described in Johnson *et al.*, *Methods Cell Biol.* 35: 73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human
15 cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C-and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ)
20 and variable excitation wavelength filters. *Id.* Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated
25 disease.

Example 7: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

Antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific
30 antibodies, at a final concentration of 0.2 to 10 µg/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described above. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced. The

coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide. Next, 50 μ l of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate. 75 μ l of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution are added to each well and incubated 1 hour at room temperature.

10 The reaction is measured by a microtiter plate reader. A standard curve is prepared, using serial dilutions of a control sample, and polypeptide concentrations are plotted on the X-axis (log scale) and fluorescence or absorbance on the Y-axis (linear scale). The concentration of the polypeptide in the sample is calculated using the standard curve.

15 **Example 8: Formulating a Polypeptide**

 The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

 As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 , μ g/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 μ g/kg/hour to about 50 mg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a
5 non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release
10 systems. Suitable examples of sustained-release compositions include semipermeable polymer matrices in the form of shaped articles, e. g., films, or microcapsules. Sustained-release matrices include polylactides (U. S. Pat. No.3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22: 547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater.
15 Res. 15: 167-277 (1981), and R. Langer, Chem. Tech. 12: 98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE Epstein et al., Proc. Natl. Acad. Sci. USA 82: 3688-3692 (1985); Hwang et al., Proc. Natl. Acad.
20 Sci. USA 77: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U. S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide
25 therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i. e., one that is non-toxic to recipients at the dosages and concentrations
30 employed and is compatible with other ingredients of the formulation.

For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides. Generally, the

formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e. g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e. g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1 % (w/v) aqueous polypeptide solution, and the resulting mixture

is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container (s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

10 Example 9: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 µg/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided above.

Example 10: Method of Treating Increased Levels of the Polypeptide

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided above.

Example 11: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and
5 separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e. g., Ham's F12 media, with 10% FBS, penicillin and
10 streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks. pMV-7 (Kirschmeier, P. T. et al.,
15 DNA, 7: 219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified
20 using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions
25 appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB 101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+aml2 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf
30 serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging

cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media.

If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

15 **Example 12: Method of Treatment Using Gene Therapy-*In Vivo***

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide.

20 The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO 90/11092, WO 98/11779; U. S. Patent 5,693,622; 5,705,151; 5,580,859; Tabata H. et al. (1997) Cardiovasc. Res. 35 (3): 470-479, Chao J et al. (1997) Pharmacol. Res. 35 (6): 517-522, Wolff J. A. (1997) Neuromuscul. Disord. 7 (5): 314-318, Schwartz B. et al. (1996) Gene Ther. 3 (5): 405-411, Tsurumi Y. et al. (1996) Circulation 94 (12): 3281-3290 (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P. L. et al. (1995) Ann. NY Acad. Sci. 772: 126-139 and Abdallah B. et al. (1995) Biol. Cell 85 (1): 1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 µg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e. g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 µm cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection

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may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice.

The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

5 **Example 13: Transgenic Animals**

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e. g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific
10 embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i. e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection
15 (Paterson et al., Appl. Microbiol. Biotechnol. 40: 691-698 (1994); Carver et al., Biotechnology (NY) 11: 1263-1270 (1993); Wright et al., Biotechnology (NY) 9: 830-834 (1991); and Hoppe et al., U. S. Patent 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82: 6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et
20 al., Cell 56: 313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3: 1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e. g., Ulmer et al., Science 259: 1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm mediated gene transfer (Lavitrano et al., Cell 57: 717-723
25 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115: 171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated
30 oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380: 64-66 (1996); Wilmut et al., Nature 385: 810813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, I. e., mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, e. g., head-to-head tandems or head-to-tail
5 tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89: 6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the
10 polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous
15 gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265: 103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

20 Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using
25 techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

30 Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than

one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to
5 both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to,
10 to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 14: Knock-Out Animals

15 Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (E. g., see Smithies et al., Nature 317: 230-234 (1985); Thomas & Capecchi, Cell 51: 503-512 (1987); Thompson et al., Cell 5: 313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of
20 the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that
25 contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e. g., see Thomas & Capecchi 1987 and Thompson 1989, *supra*).
30 However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e. g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (I. e., animal, including
5 human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e. g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence
10 associated with the polypeptides of the invention, e. g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the
15 control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e. g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the
20 body, e. g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U. S. Patent 5,399,349; and Mulligan & Wilson, U. S. Patent 5,460,959 each of which is incorporated by reference herein in its entirety).

25 When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the
30 introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function

of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

All patents, patent publications, and other published references mentioned herein
5 are hereby incorporated by reference in their entireties as if each had been individually
and specifically incorporated by reference herein. While preferred illustrative
embodiments of the present invention are described, one skilled in the art will appreciate
that the present invention can be practiced by other than the described embodiments,
which are presented for purposes of illustration only and not by way of limitation. The
10 present invention is limited only by the claims that follow.

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CLAIMS

We claim:

1. An isolated nucleic acid molecule comprising
 - (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes
5 an amino acid sequence of SEQ ID NO: 165 through 280;
 - (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID
NO: 1 through 164;
 - (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid
molecule of (a) or (b); or
 - 10 (d) a nucleic acid molecule having at least 60% sequence identity to the nucleic
acid molecule of (a) or (b).
2. The nucleic acid molecule according to claim 1, wherein the nucleic acid
molecule is a cDNA.
15
3. The nucleic acid molecule according to claim 1, wherein the nucleic acid
molecule is genomic DNA.
4. The nucleic acid molecule according to claim 1, wherein the nucleic acid
20 molecule is a mammalian nucleic acid molecule.
5. The nucleic acid molecule according to claim 4, wherein the nucleic acid
molecule is a human nucleic acid molecule.
- 25 6. A method for determining the presence of a breast specific nucleic acid
(BSNA) in a sample, comprising the steps of:
 - (a) contacting the sample with the nucleic acid molecule according to claim 1
under conditions in which the nucleic acid molecule will selectively hybridize to a breast
specific nucleic acid; and
 - 30 (b) detecting hybridization of the nucleic acid molecule to a BSNA in the
sample, wherein the detection of the hybridization indicates the presence of a BSNA in
the sample.

7. A vector comprising the nucleic acid molecule of claim 1.

8. A host cell comprising the vector according to claim 7.

5

9. A method for producing a polypeptide encoded by the nucleic acid molecule according to claim 1, comprising the steps of (a) providing a host cell comprising the nucleic acid molecule operably linked to one or more expression control sequences, and (b) incubating the host cell under conditions in which the polypeptide is produced.

10

10. A polypeptide encoded by the nucleic acid molecule according to claim 1.

11. An isolated polypeptide selected from the group consisting of:

(a) a polypeptide comprising an amino acid sequence with at least 60%
15 sequence identity to of SEQ ID NO: 165 through 280; or

(b) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1 through 164.

12. An antibody or fragment thereof that specifically binds to the polypeptide
20 according to claim 11.

13. A method for determining the presence of a breast specific protein in a sample, comprising the steps of:

(a) contacting the sample with the antibody according to claim 12 under
25 conditions in which the antibody will selectively bind to the breast specific protein; and

(b) detecting binding of the antibody to a breast specific protein in the sample, wherein the detection of binding indicates the presence of a breast specific protein in the sample.

30 14. A method for diagnosing and monitoring the presence and metastases of breast cancer in a patient, comprising the steps of:

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(a) determining an amount of the nucleic acid molecule of claim 1 or a polypeptide of claim 6 in a sample of a patient; and

(b) comparing the amount of the determined nucleic acid molecule or the polypeptide in the sample of the patient to the amount of the breast specific marker in a normal control; wherein a difference in the amount of the nucleic acid molecule or the polypeptide in the sample compared to the amount of the nucleic acid molecule or the polypeptide in the normal control is associated with the presence of breast cancer.

15. A kit for detecting a risk of cancer or presence of cancer in a patient, said kit comprising a means for determining the presence the nucleic acid molecule of claim 1 or a polypeptide of claim 6 in a sample of a patient.

16. A method of treating a patient with breast cancer, comprising the step of administering a composition according to claim 12 to a patient in need thereof, wherein said administration induces an immune response against the breast cancer cell expressing the nucleic acid molecule or polypeptide.

17. A vaccine comprising the polypeptide or the nucleic acid encoding the polypeptide of claim 11.

20

SEQUENCE LISTING

<110> Salceda, Susana
Macina, Roberto
Recipon, Herve
Pluta, Jason
Sun, Yongming
Liu, Chenghua
diaDexus, Inc.

<120> Compositions and Methods Relating to Breast Specific Genes and Proteins

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<212> DNA
<213> Homo sapien

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 <211> 319
 <212> DNA
 <213> Homo sapien

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319

<210> 6

<211> 4261

<212> DNA

<213> Homo sapien

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<211> 539
<212> DNA
<213> Homo sapien

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<210> 8
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 <212> DNA
 <213> Homo sapien

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<210> 10
 <211> 626
 <212> DNA
 <213> Homo sapien

<400> 10
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12

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<212> DNA
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13

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<210> 12
 <211> 744
 <212> DNA
 <213> Homo sapien

<400> 12
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 <211> 799
 <212> DNA
 <213> Homo sapien

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15

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aaaaaaaaa ttggcggcc 799

<210> 14
<211> 456
<212> DNA
<213> Homo sapien

<400> 14
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gagtgtggag tgagcaagac ccaaatcgga gcttcatccc tgcattggtt attttgccta 420
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<210> 15
<211> 282
<212> DNA
<213> Homo sapien

<400> 15
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attcatattg ctattgtaat attaatatat agtaattaac tacacatgac acagctttac 180
atgaccttaa gtagttatca acattaccat aatagtaata ttaataacta caataagagc 240
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<210> 16
<211> 2658
<212> DNA
<213> Homo sapien

<400> 16
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16

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<210> 17
<211> 493
<212> DNA
<213> Homo sapien

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<400> 17
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gaggaggaac aaacaaaaat agacatcatt ataaaaaata cccaagactt ttagatgttt 480
ctctaacatt tgg 493

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<210> 18
<211> 1412
<212> DNA
<213> Homo sapien

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<400> 18
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agatttgctg tataaagata aataggaaat tgctcttctt cccacgaaac tcaaaacatt     1380
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<210> 19

<211> 383

<212> DNA

<213> Homo sapien

<400> 19

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19

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catatttctg actttaatgt aactcactct tattccgtag tcacatgttt gctgctcatg	240
gttcacatta catttattca gcatctgctt gagccaaggc actgtaacta catgtttttt	300
ttagttacct actttgtaag gtctgtttc ttggctacat ctgattacag taaacatagg	360
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<210> 20

<211> 1804

<212> DNA

<213> Homo sapien

<400> 20

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20

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<210> 21
<211> 252
<212> DNA
<213> Homo sapien

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<400> 21
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ggataaaccc ctcatgatca taatgaataa tgatgtgtgg agagtgggga gggthttacat 180
atgaaaaatg tagaaaatac aaaaagtgtc tatatataca aaatgtaagt gthaacattt 240
ttatatttgc tt 252

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<210> 22
<211> 1595
<212> DNA
<213> Homo sapien

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<400> 22
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<212> DNA

<213> Homo sapien

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22

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23

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26

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30

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<210> 29

<211> 477

31

<212> DNA

<213> Homo sapien

<400> 29

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tgtgagtttt atcagtttgc cattaggtag ttgtgtgcac ccttgggcat atagcacttt      180
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tggaacaaca aaaacaaca aaaaacaaca aaaaaacagc ttgggcggct acttcggtgg      360
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<210> 30

<211> 662

<212> DNA

<213> Homo sapien

<400> 30

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<210> 31

<211> 780

<212> DNA

<213> Homo sapien

<400> 31

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32

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<210> 32
<211> 597
<212> DNA
<213> Homo sapien

<400> 32
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<210> 33
<211> 2328
<212> DNA
<213> Homo sapien

<400> 33

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tggcggtggcg gcggcgcgaa gccggcgctcg gggctcgcgg cgtggtggct ctggcgttgc	180
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<210> 34
<211> 737
<212> DNA
<213> Homo sapien

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<400> 34
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attgtcaaaa actgctgtta ttaacttcac ttgagttggt taacttcctt ctgttttaag 540
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catagatgaa atacattgga aaaaaaaaaa aaacaaaaaa aaaaaaaaaa aagcttgggg 660
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ttccaaacaa aaaatca 737

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<210> 35
<211> 215
<212> DNA
<213> Homo sapien

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<400> 35

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35

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cctatttctt tgtaatttac tatagcactg atgacaaagc atagacatac aatgagaaag 180
agcaaatcag catatcagtg tgactgtgca accac 215

<210> 36

<211> 1065

<212> DNA

<213> Homo sapien

<400> 36

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<210> 37

<211> 872

<212> DNA

<213> Homo sapien

<400> 37

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acgagacacg accacaaaag cgaaaagaaa gagagaatag cacaacgata aaagaaaaca	780
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<210> 38

<211> 751

<212> DNA

<213> Homo sapien

<400> 38

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<210> 39
 <211> 2299
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (275)..(275)
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<400> 39
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<212> DNA
<213> Homo sapien

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<212> DNA
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 <213> Homo sapien

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 <213> Homo sapien

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tagatctatt ctgaagctgt tcatttttaa caaataaaat gttacagggt tcacatgatt 3420
tattctcagc tctaaaaaaaa aaa 3443

```

<210> 48

<211> 670

<212> DNA

<213> Homo sapien

<400> 48

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gCGTggcgCG gccgaggTAC tccagcctgg gagacagagt gagactccat atcaaaaaaa 60
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tgacagcgta aatagaaaaa ttaatacatt tgaaagataa agttgaaata tccctataat 180
gtggaacaga atgacaaagg gacatgataa tgaaccaaag gtgataggag ataaaaaaaa 240

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ttagaatatt aagtcaaaag atgtaatatc taactaataa tagaaaacag aagagaagaa 300
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cccaatgatt aaaaaagat taataggcat atttgtgaat tttagaaaag gcatattcgt 420
taatctctac ggacaatcaa tcacaacaaa caagcacaca aacacacaac aaagaaccgc 480
cttcggcgag aaaccacacg gggccaaaga acgaaaggga ccaccggggg gcgagacatc 540
tggtgatacc acaccaggca caaacaatca tcaccagcaa aaactatcag cgaagcaaac 600
gaagaagaac aaaacacaga caaaaaacaa aagaacaaga aacgaagaca caaaaaaaaa 660
caacaaacag 670

```

```

<210> 49
<211> 973
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (234)..(398)
<223> a, c, g or t

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<400> 49
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ttgagactga tgctagaata acaacagtag aagtgattat ttctgataat ggggattaga 180
atgtgtaatc ttctgggga aaatacttgg ctaggttggt tgtaggcaat ggtnnnnnnn 240
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 300
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acatgacagc gtaaatagaa aaattaatac atttgaaaga taaagttgaa atatccctat 480
aatgtggaac agaatgacaa agggacatga taatgaacca aaggtgatag gagataaaaa 540
aaattagaat attaagtcaa aagatgtaat atctaactaa taatagaaaa cagaagagaa 600
gaataaaaga aataataaaa gaaaatttcc ccgaactgaa ggcattgtctg tagtttgaaa 660
ggaccaatg attaaaaaaa gattaatagg catatttgtg aattttagaa aaggcatatt 720
cgттаатсtс tacggacaat caatcacaaс aaacaagсac асаасacac асаааааас 780
cgcttcggc gagaaaccac acggggccaa agaacgaaag ggaccaccgg ggggcgagac 840
atctggtgat accacaccag gcacaaacaa tcatcaccag caaaaactat cagcgaagca 900

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aacgaagaag aacaaaacac agacaaaaaa caaagaaca agaaacgaag acacaaaaaa 960
 aaacaacaaa cag 973

<210> 50
 <211> 1019
 <212> DNA
 <213> Homo sapien

<400> 50
 ataggaatgg ctctaatacat gctgagcggc gcaggatgatg gatcgcgggc aggtacaagt 60
 ttagagcagc ctagctcgag tcctcaaccc cagtcctctt agaagtgaac tgattgcact 120
 ggatccctaa acccaaatg ttgaggacac atgtgatgac tccacttgct caggccagct 180
 ggctctctgc actttccct gccaccact tgtaactacc acttaattat cttgtgttaa 240
 ttgctttgtt gtgttgggtc tgtatttttg tggtcagtgc ctgcaggcag aaatgtgaaa 300
 gcatttggtg tgttgaagat acttgcttct tttttaataa aattaaaagt gcagcacgta 360
 agtatgatac tgtgtagttt tttgacacaa ccatgagata caataagcag ctttgactta 420
 gtgtcccaa aagtggttct tggctacag caggggcaaac atatatgtgg caagttctga 480
 tcacatactt ttagacagaa agaataaaaa attcatatcg catggctttg tagcctaaga 540
 gcacagaatc atacacgtgt gttaggagaa acattcattc tcacgcatat aaactggctc 600
 ctggcagagt agggcagtaa gtgggatcaa aggtgaattc accttatttt cagttggtag 660
 agtatggaca atatatcact tatttgaaaa tacctgaatg gaaaccagc ctctactact 720
 gtacttaaca ctgggcagtt acttgcttct cctgagccct caaatttttc tttctctgtt 780
 agaatgggat ttatgccacc tacgggggtg cagtgcctac aggggctggg cagccacgga 840
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 tttctcaacg ccgagtttag tttttaactc cttagttggg ggccttgctg ctcccagctt 960
 tattaggagg gaggctaag ggagggggcc cggtcagtgg cgtgtcgtgc ccataaat 1019

<210> 51
 <211> 2169
 <212> DNA
 <213> Homo sapien

<400> 51
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 aaaaaaaaaa aagaaagaaa tgtgttgctg gtatcagata tcagaccaag aacacttcag 180

tctctctaag gatgccctga gctacctcac tgttaaagga cgacatcaac acagaatgca	240
ctaaacagga aataagctgt aatctagaga atttccatta tgtgttactt tttggtgact	300
aacatggaat gttgaaaagg aagagctgga aagctcagtt gttttccttg ttcctctgac	360
attgtccagg caagagggca tcctgatcag atgagtagat ttggctgaga aaaaccctag	420
agtaaggcag gcactttgtg gaggtggatg atgatggctc ataaaaacgt ttgttctcag	480
tccagttcag ggctctgcca gcagtcttcc agatttgaac tgcttaaaca aaccctacag	540
ataaattggc actctgattt gtaattctgt ttgtacaagt ttagagcagc ctagctcgag	600
tcctcaaccc cagtcctctt agaagtgaac tgattgcact ggatccctaa acccacaatg	660
ttgaggacac atgtgatgac tcacttgct cagccagctg gcctcttgca ctttcccctg	720
cccaccactt gtaactacca cttaattatc ttgtgttaat tgcttttggt gtgttgggtc	780
tgtatttttg tggtcagtgc ctgcaggcag aaatgtgaaa gcatttggtg tggtgaagat	840
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agaataaaaa attcatatcg catggctttt gtagcctaag agcacagaat catacacgtg	1080
tgtaggaga aacattcatt ctcacgcata taaactggct cctggcagag tagagcagta	1140
agtgggatca aaggtgaatt caccttattt tcagttggta gagtatggaa aaatgtatca	1200
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cttcggtaaa ctggagcaca tgattcctgg gaagcaggcc tagtgtaaac aatttatatt	1440
tctagaaaag acagaagttt agagtatatg aaatctaatt tttaagtatt gggtggcaac	1500
taattgacta tcgtctacca taaggttata tgataattat tagggcagga gagtgaatgc	1560
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aatccatttt tataaaattt ttgtaataaa aattcacttg atcacttgcc tgctttcttt	1800
taaacagtgc caagcgtaat gcccttgat aatttacata tatgtgaacg tggctgtgat	1860
agctgctgat gttcacacat aggccatctt acatgtaatg attccatggt tggacttaaa	1920
cagcttcaca catttattgt acagttaggt gtcacatgct ttacttttt attttataat	1980

ctgtatttct gtgaggtaga cattattggc tccatgttat atacattgat agcccggagc 2040
tagagattga acccaggcca tcctccccac tgcctttcat catcaacaca accaccacca 2100
acagtatttt aaaagtgtta aatattggca gacgtgtcat tgttctgagc actaggacta 2160
gggcttatg 2169

<210> 52
<211> 919
<212> DNA
<213> Homo sapien

<400> 52
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caagatgcaa tccctctcaa gaactgtata atctagtaag agcacatata gagatgggtgc 120
ctgcaggtaa aaactgctct gaaacatgg ggagagaaga gtttacttcc ttccagaggg 180
tgaagtcggg acccatttaa atttggtagt atgggtgagg aaggtcataa cacgctaagt 240
aaactgggtgt ctaagcatgt gacggcaaca gctaattggtc tagttcctcc atggctttaa 300
atgcatgaaa gggaaaagag tattcaaagg tatttttatt ttatctcatt gttagcccag 360
tataaggcag gatgacaaaa aataaataaa agtatgaaga ggcaagaaca tagattgaaa 420
actccatttc ctagtttttag tgtaaactca atcccttggt catatacatc tagttcctga 480
agtccacact gccaaaaggg aaaaacaaga aaaaccagcc ctagcagtgc cctgtcatca 540
tggcagagca ctgtctcttc tgtgggactg aaacagctag ctttggtac tgccggtagt 600
ggaccaatat ggcacatgga aattaaaaag tcccataaaa cgtgccctcc taacacgaga 660
ataagaaagg tggctgaagt agataatttc agtgacggag ggggatgaaa tatttttgggt 720
ttatttgatg tatgatgacc cactatgctt attcctatct taaaaaccag atgagcagtc 780
tctgacaatt tctggtggtt acttcctcaa tgatttgggc tttctcccct ccggtttgct 840
tccttccctg tttttgttct ggcttcctta cagctccttt cccactgag ggggttttct 900
gagaacttct cccttccta 919

<210> 53
<211> 1611
<212> DNA
<213> Homo sapien

<400> 53
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tcttggacct gccttcttct attgcccccc ccacatggt taaaattttt cgcccccccc 120

51

caattttttt tttttttttt ttttagacat gaccaattta ttcagagaat tcaaatttcg 180
tttggcaaag tatatccggg gcagagagtt tgggataatt atgtcattgg aagcaatcac 240
attatctaca gcaaattgcc tggggtagta tctgaaggaa aggcaaaact tttaaaaaca 300
atttagtatg tgggggggtg ataatacata atatttgcaa aggtaacaaa acaacaacc 360
agcttataca accaaggcac aaaatatgct aatgctaata atcctttatt caatttagct 420
caacacacat taagtactta atttgtgcaa gagactgggc tatgtgctgg gggtgagggtg 480
gaaatacaaa aacaccaaga tgcaatccct ctcaagaact gtataatcta gtaagagcac 540
atacagagat ggtgcttgca ggtaaaaact gctctgaaac catggggaga gaagagtta 600
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cataacacgc taagtaaact ggtgtctaag catgtgacgg caacagctaa tgggtctagtt 720
cctccatggc tttaaattgca tgaaaggga aagagtattc aaaggatttt ttattttatc 780
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atattattca tcaccttaa cttctgaaag tttggtttat gttatcttat ctagaaagaa 1440
aactacttac aaatctcatt ttcccacaaa attaattcaa catccaatcc ttaaaaaataa 1500
ataaagcttt gccaatggta aattggaatg catatacttg ccaggctttg atgaaataaa 1560
aataaacgat ttacataagc agtacctggt aaaacaaaaa cctccttttg a 1611

<210> 54

<211> 859

<212> DNA

<213> Homo sapien

<400> 54

actcctcact cagaaacaag aacagcgaca gcccttctcg agcgagatga cacgagctag 60

52

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caaggtggag gacagacaca ggagaaataa aacagagatg atgctcgcta ggaatccttc 180
ttataaaata ttcaacatgt tattattatc ctcgtccccc agaggggtgg ttgatccatg 240
gatagaccta aagaagaaaa gaacatcaat ccagcatata aactccatag aatagtcaaa 300
ggtcaggtgg gacgcgaaaa ccgatcaaat cgcacctagg ttacgcccac ggccgatcag 360
cccaacctcc acctctggag ggtcccccag agaccctcgc ccgacgctag acccgaggga 420
gcctcagcta agggcgcccc tgcagaagaa tcggctatgt cttcgattga tggagagcag 480
gagagatcgg cagagtatat ggttcggcta ggtgaagtag tttatcttca tatcccactt 540
aagatccgta tagcttacta aagctctgta gtaatccccg acaaaaggga aaaacaagaa 600
aaaacagcct ctgggcgagt gccccctggc atcatggcga tgacccgcgt gtcatacttc 660
gtgttgccgc actgaaacag cctcacgctt agctttcccc cgcccccgag tattgggacc 720
attattggca catgggaaat ttaaaaagtc cataaaccgt gccctcccta acacgagaat 780
aagaaagggt gctgaagtag ataattccag tgacggaagg gggatgaaat attttgggta 840
tgaaggatat atgactcca 859

```

<210> 55

<211> 748

<212> DNA

<213> Homo sapien

<400> 55

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gtaacaatat attcacactc ggcaaggcta gaatattgaa attatggcca acattgctta 120
ctttaagatt gtttacttta taaagaagct agagtagttg tgcaactaga acagatgttt 180
ttaaaatggt tgccattcaa agataggctt ggtgggacaa aactaatatg catactacat 240
acatatatct cttgtcttct ttactgtcaa tctttcagaa cagtaacatg acattacaaa 300
cacctcaaat tcccacttca aaatgaacag aaaaatggaa aaacattatt tcccatttca 360
taaaattaaa aatcaagtca gaagagaagt aaaactcatt tttatgcatt taacttaaaa 420
gcctgaatac acgactcctc ctagagagaa ggaagccaga acttcagaag tagccagtgg 480
tccaaagaat aaatggcccc atgaccttct ctatggttca tgacttactg agggctgatg 540
caaactctgg caagttatctt ttcattgattt ccaaggatct gggatatgta aacgaaatga 600
ttaaaagaca tttctctgaa tttgcaagaa gacgactgaa gaatcagaac aaagatccaa 660
cggcctttca cgtggctaca tggtcaccat tacaccacaa ctcaaaaccc acaggcgagc 720

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tttctctcaa atacacattc caaatggt

748

<210> 56

<211> 2408

<212> DNA

<213> Homo sapien

<400> 56

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aaaataagtc tctatgaatc cttattaatc atttgaaatt atgctataat atttttttaa 120

actcacctgt ttggttctgg gtgaagcagt tcctgaagga gtgttttgtc agaatatatt 180

gttaggtgaa tagaggggtc tgtggccaag taagtgtggg aaatagtggg ttagacaaaag 240

ttgagttact gttggccttt cagacctttg atacgctaata gtgcatttta aatctccaag 300

aagcacctct attttataca tcatttccct aatttatttt aatatggatt tcttgttttt 360

gttttcttga gacggagtct tgggtcttgc acccaggctg gaggcagtg gcacgatctc 420

ggctcactac aacctccgcc tcccagggtc aagcgattct cctggcctca gcctcccaat 480

ttactgggat tacaggcacc tgccaccacg ccagcctaata ttttgtattt ttagtagaga 540

tgggggtttca ccatgttgac caggctgatt ttgaactcct gacctcaggt gattctgccc 600

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accaacttgt atttccagaa caattttcca aaccttttct ggctgtactt taaaagtgcc 1080

aaaaaggcaa tgggtgttta tgacactaaa gtcacatata agctagtatg atacatacat 1140

catagaaagc ttatagttgc tcagtacaa agcaaaggaa gtttaattatt ttccagtttt 1200

gttcattacc gaagacagtc tacggttcat agttttcact aaattctaag cagattctat 1260

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aaagctcgcc tgtgggtttt gagttgtggt gtaatggtga acatgtagcc acgtgaaagg 1500

54

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ccgttgatc tttgttctga ttcttcagtc gtcttcttgc aaattcagag aaatgtcttt 1560
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ttatgaaatg ggaaataatg tttttccatt tttctgttca ttttgaagtg ggaatttgag 1860
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tgtatgtagt atgcatatta gttttgtccc accaagccta tctttgaatg gcaaactttt 1980
taaaaacatc tgttctagtt gcacaactac tctagcttct ttataaagta aacaatctta 2040
aagtaagcaa tgttggccat aatttcaata ttctagcctt gccgagtgtg aatatatttt 2100
actcagagac tatgtacaaa taaactaaag tggatgaggt gatcaatatt gtaaagaatt 2160
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tcaaatctcc tgaaaaaaaa tcagaaataa caagaagaat gggggggcac gggctataaa 2280
tttttaaaaca ctttttgggg ggggcccag ggggtggacac ggggtgttcc agagactggg 2340
ccaaaggggtg gggtcccaaa aaacgggggc gaggcgcaac cggggggggg gcttcaaaag 2400
aagagggtg 2408

```

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<210> 57
<211> 892
<212> DNA
<213> Homo sapien

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<400> 57
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gagatagcta tgagaaaact aaaactgcta tgagatagaa atgatgtaaa attatgtgga 180
aagttttccc tcatatactc acatacagcc tttgaagggc tctggctctg accggttgat 240
ggccttgagc gagatgaaat catgaaattg agtcaaatca atttgacatt gaaatgacaa 300
gaggaaactc ttaaatacat aaaaacaagc tctcatttgc ctaggataga tactgtctta 360
aaaataaaga ctgaacctag atgttctgag cactagcaac aaggatattt aacaagttaa 420
aaggaattct ctgaaaaagt tataaaatta ttctaggaaa cataaccata atagtgtttt 480
aagggacttt cacctgggga ttttatattc atgaacagag tgtattctgt atttaaaatg 540
tctcatttgt ggggaattgga tgacatgttt tttgataaat ttattcgcaa tataaattga 600

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55

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ctttttattc taggaccatg tgaatcatgg gttccattgc acaaatacaa atattttaat 660
agcttccttag gcagtgggtg agacatcttg gatataatca ttgtagatct tgtatatttg 720
attttttaag aaacctaaat aaacagagag gcataaacat atcttagagt caagtggtag 780
tgtttagcat tggatataac tactgggtgt ttcaacacac aaaaaaaaaa aaaagcgggg 840
gacctgccca tccttcctgg tgaattttcc cccacacaaa aacaaaacag tt 892

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<210> 58

<211> 3788

<212> DNA

<213> Homo sapien

<400> 58

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ttttcgcgct ctgaaatcac aggcctgaca taggagcaag gcctcgatat atagccgccg 120
tgtttttgta aggaatcgtt cgcacaaact ttatagaatt tccccattt gtagagaaag 180
aatcgcgtag gaaaaccatc agctacagga taaaataag ataaaatgtg taatcacaat 240
tcattactac aagatgtgag ttactactac cagcacacta gtatacatat tctttgggag 300
aagggcatcc agacctgcta acctcatata gatcccattg gacaactgga tgtacaccag 360
gttttttaat aaaaatgggc caaccactgt cttttcagaa tcaaatgcag acaatggaaa 420
aattatggta ttaaccttca caagtttgag cctcccccaa ttatgccacc agttttacaa 480
ttttaacagc cttctacat acactccatc ttctctatct tagttccaag ttttagtttt 540
caatcccat tataccatt ccatgtgtta ttttaagaaa aaaccttccc agttagtgtg 600
cagaaactat gatttagctt accccctcca ctaccagcc aactacagag aggatggagt 660
gtaatatgag ccgtacagag tcttaatgcc attcatgagg accacttagt cttacatga 720
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56

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aactcggc 3788

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<210> 59
 <211> 432
 <212> DNA
 <213> Homo sapien

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<400> 59
gtgactgact catatggcga atgggtgcact gatgctgccg agcggcgagc tgtgatggat 60
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tttgaataga tggcattatc actttattgt ttttttaaca aaaacttttt ctcaattatt 180
ctattgcaat gttattctga gcaagtccta tgccaaatat cttgtataat gtttgtatgg 240
aagattaaat ttactcttg tatggtaaga ctatttcagt tactgatttt atagttggaa 300
tttgatattc cagcacaag tccacagtgt attcagaaat ccaagttggg gtcatacatt 360
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cgttttgaca gt 432

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<210> 60
 <211> 1123
 <212> DNA
 <213> Homo sapien

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<400> 60
caagtgtccc atggattaag attaggtcgg gaggtttagg agtgatccag aatgacctcc 60

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58

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cagaattact gtgcgtacaa ctttattttt cagagttttc atggaatggg aagagtttta 120
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gcataaattt tctataatca ggcacctttt gctgcttttg agtaagactg ttttcctggt 300
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<210> 61
<211> 676
<212> DNA
<213> Homo sapien

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<400> 61
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gtatgaaagt catcataaca gatgttttcc aaaaacttgt agaaggttgt gaaaaaacta 180
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catgttttaa aatacttctg cttcgttacc tcaagtgtgg catgcagcat tttggaagga 300
aaattgaaga cgtgttcaag aaaacatgaa cagaagcaaa tgatgaaaat gagcatttta 360
cttgatgttg ataacatcac aataaattat ggagacaaaa tacatatttg gctaactttt 420
aattgctgaa caataaagtg ttttctttta agatcaacaa caagaagaac atgaaaacat 480

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59

cgaaaataat gaaaacataa caggcttggt gggactcca gtggcacata ggggtgttcc 540
cgtgtgtgtg gcaagttggt ttctccgggc tccagttccc ccacaattct cgcggcacac 600
agggggaagg gtacctgat acaatccccg acatcggtag acaaccgtac agcatcagtc 660
gggacattga actagt 676

<210> 62
<211> 883
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (870)..(870)
<223> a, c, g or t

<400> 62
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ctaaattggc aagaattcta aagctgaatn tatatctggg tga 883

<210> 63
<211> 795
<212> DNA
<213> Homo sapien

<400> 63
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cggccgggaa tgtcc 795

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<210> 64
<211> 951
<212> DNA
<213> Homo sapien

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<400> 64
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tgggttaaacc agtgggcaca gattacttat cttccttctc tgctttgtga ctaccagca 240
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tcttaatttt aaaatatgct gatatgcctt aaactgtagt tgtagatcct tgtccatttg 660
ctgtttgaaa ataaccaatg tgttttctaa aactgtcgtg taatctactt tcattgttaa 720
tgagaattg tcatatatgt aagccgcatg ttagacattt gtctttttta aactaaagta 780

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attgtattga tgtgaagcat atcatttttt caaatatgaa agtgatcact tagcaacatg	840
cttggttaatt tggcatctgt taaggtagga gagtgggtgaa cagataatct atgcatatat	900
cactagtgcc aagacataaa gcgggggaaa atatattttt acccaaacat t	951

<210> 65
 <211> 1666
 <212> DNA
 <213> Homo sapien

<400> 65	
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 agggaagtcc tcgagaagga catacagga aagcctaata caacagaggg aagatcccaa 1620
 ggaaaagcac tatcatataa ataattatcg ccgccggctg tgcggg 1666

<210> 66
 <211> 425
 <212> DNA
 <213> Homo sapien

<400> 66
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 agctt 425

<210> 67
 <211> 1342
 <212> DNA
 <213> Homo sapien

<400> 67
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 ggctgttttg gctaggcact gctaatagct gctctgcaaa aaggggcaaac ataaaagggc 180
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 acaatgttct ctcatTTTtg taagagtgca gcccctcct taatttccac tgggtgcttg 480
 ggtagaatgg ggcacctggg gaaacttaag ctggaagggc atcatgaaaa gtgacagata 540

63

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cactaattcc tttggtgggt ttctttgtag aaagacaagg cactctctcc acagcagccc 600
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gtgtggtaca gagctcagtg cacagagtat tcaccagca tcatgaatca acttgggagg 1260
agtcaaccaa atgaacaatc taccaaaaat ttcaaataaa gtcaaaccac ccacaaaaaa 1320
aaaaaaaaaa aaatgagcgg cc 1342

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<210> 68
<211> 567
<212> DNA
<213> Homo sapien

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<400> 68
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ggattattta tggcaatcca ttttctacag aatttgaatt ctaaggccat ttgagggtggg 240
aagtaagtaa atagagctaa gaatgcctgg aaacctcagg cacttagaat ttttttatca 300
tcgggtagtg aggtacaggg atggtgcaaa ataaatattt aaagtagagg aaattccatt 360
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tatgattcca cagaacaact gtgtaaactt ttaaataaat ttaagctggg ctcaaaaaaa 480
aaaacaacaa aaaaacaaaa ccgtggcgga aaccggggca aaaggagccc ccggtggaga 540
atggctcccg cccaattccc aaaaaag 567

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<210> 69
<211> 1007
<212> DNA

```

64

<213> Homo sapien

<400> 69

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cacagctgga agtggcagag cagttgggtg accctaccca aaggaaagat agatgtgttc      60
ctggccagtg caggggtgag atgtgagcac agctgcatgg ccatgctgct gtcttgggtc      120
tttgtcggag gggattcaga agtttagaca gaggtcattg cccagatcag ttccagtgtc      180
acatgatgct ggtggtcatg acttgcaagg gtgggttcctg ggccatcagt gagaataaca      240
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aagatactta agtgactaat tctattagtc cttgttgact gtgattctat taatggcaaa      480
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actgaggatc aaactatatg attcccagaa caacttgtaa actttttaa atattttaaagc      780
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attcagggta ggtgtggaaa actgtgagta gatacaggac ttaaagggtg gaagatgggg      900
aagtatagga aggcagtga aaactaaatt gtaaaggctt tgagtgtgag gttaaagaaa      960
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<210> 70

<211> 568

<212> DNA

<213> Homo sapien

<400> 70

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agatgctgcc gagcggcgca gtgtgatgga tagtccaaaa aaaaaaagta ttaaaatgtg      60
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<211> 260
<212> DNA
<213> Homo sapien

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68

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 <213> Homo sapien

<400> 75
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<210> 76
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 <212> DNA

<213> Homo sapien

<400> 76

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70

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<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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<212> DNA

<213> Homo sapien

<400> 82

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<211> 607
<212> DNA
<213> Homo sapien

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<210> 84
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<212> DNA
<213> Homo sapien

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<400> 84
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76

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 <213> Homo sapien

<400> 85
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<210> 86
 <211> 5119
 <212> DNA
 <213> Homo sapien

<400> 86
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80

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<210> 87
<211> 489
<212> DNA
<213> Homo sapien

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82

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<210> 89

<211> 520

<212> DNA

<213> Homo sapien

<400> 89

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83

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<210> 90
<211> 2395
<212> DNA
<213> Homo sapien

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<400> 90
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84

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<210> 91
 <211> 522
 <212> DNA
 <213> Homo sapien

<400> 91
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85

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<210> 92
<211> 1271
<212> DNA
<213> Homo sapien

<400> 92
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<210> 93
<211> 679
<212> DNA
<213> Homo sapien

86

<400> 93
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 <211> 994
 <212> DNA
 <213> Homo sapien

<400> 94
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<210> 95
 <211> 496
 <212> DNA
 <213> Homo sapien

<400> 95
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<210> 96
 <211> 3175
 <212> DNA
 <213> Homo sapien

<400> 96
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88

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<210> 97
<211> 641
<212> DNA
<213> Homo sapien

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<400> 97
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<211> 2231

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<212> DNA

<213> Homo sapien

<400> 98

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ggttccggtg gaggaggagg ttgctggtga tctctgctcc taacgatgaa gactgggcct 1860
attcacagca gctctctgcc ctcaagtggc aggcgtgcac attggtctgg gcgccttacc 1920
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cccgagataa cgagaaacgt acaccccatg gtgaaaaaca ccgcacaaat ccacggaccc 2040
ggagacaacc caggccaggc gcaaaaagca agaccacacg gatatcacc aaggcagcga 2100
gaagggacca cacacacacc cgcacaacag gacacccaag cggcgccaca acagtcacga 2160
caccacaagg ccacgaagca acacacagaa acatacacag cagcacacgg ccatacaacc 2220
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<210> 99
<211> 488
<212> DNA
<213> Homo sapien
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<220>
<221> misc_feature
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<223> a, c, g or t
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<222> (372)..(374)
<223> a, c, g or t
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<222> (384)..(384)
<223> a, c, g or t
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<220>
<221> misc_feature
<222> (387)..(388)
<223> a, c, g or t
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<220>
<221> misc_feature
<222> (424)..(424)
<223> a, c, g or t
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<220>
<221> misc_feature
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<222> (433)..(433)
<223> a, c, g or t

<220>
<221> misc_feature
<222> (443)..(443)
<223> a, c, g or t

<400> 99
ccgggcaggt acccaccat aaaattatga gtgtaaaagc actttgcaa ccttgatact 60
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tttccgctgc ccacctgtca gctatgtgag gcctaaagag agggagggct aggccattcc 180
tcagcttctg aggttcctgg cccttttccc ctcccatctg tccacagctg actgctaagg 240
ctggatgcgt aggggaaagc agagaaaagg tgatttactg ggacacagag acacaggctg 300
gaacgagcat acgcgatgtg ctcttcctta acaatttctg aaggccattt ttggctgggn 360
nncacagtgg cnnntcacac ctgntannat cctgcactt tgggaggtaa aggcagagga 420
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<210> 100
<211> 558
<212> DNA
<213> Homo sapien

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<222> (430)..(432)
<223> a, c, g or t

<220>
<221> misc_feature
<222> (442)..(444)
<223> a, c, g or t

<220>
<221> misc_feature
<222> (454)..(454)
<223> a, c, g or t

<220>
<221> misc_feature
<222> (457)..(458)
<223> a, c, g or t

<220>
 <221> misc_feature
 <222> (494)..(494)
 <223> a, c, g or t

<220>
 <221> misc_feature
 <222> (503)..(503)
 <223> a, c, g or t

<220>
 <221> misc_feature
 <222> (513)..(513)
 <223> a, c, g or t

<400> 100
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 accctgatac tctatgaaga agtaaaaagt agtgctgtaa ttattatcat tattatgtcc 180
 aatgggttgag gtttccgctg cccacctgtc agctatgtga ggcctaaaga gagggagggc 240
 taggccattc ctcagcttct gaggttcctg gcccttttcc ccttccatct gtccacagct 300
 gactgctaag ctggatgctg aggggaaagc agagaaaagg tgattttactg ggacacagag 360
 acacaggctg gaacgagcat acgcgatgtg ctcttcctta acaattttctg aaggccattt 420
 ttggctgggn nncacagtgg cnnntcacac ctgntannat ccctgcactt tgggaggtaa 480
 aggcagagga tttncctggt gtncccaagc agnttacgag tgcctggcca gctggaagcc 540
 tactgcactc tgttggcc 558

<210> 101
 <211> 799
 <212> DNA
 <213> Homo sapien

<400> 101
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 tcccaggctg tgctttgacc ctagggatac cctggctatt aagataaaaa gatttgtgga 120
 cattaaaatt atgaatatgt cagtaataat ccagcacaca ttgaaatatt gacacagatt 180
 accataattt gtgcaacatc ttataaacia tgctatttcc acagtagtct aaggcttcac 240
 cagcctggcc cactgtatct agactttagg ttcattttta ttaattatgc tttccttctc 300
 tgtatcattt gggaagttga taaatatcac ttccttagat accttcattc agtgatatat 360
 ctggctttta caattaaatt ggaaaaggta agtttctctt tgggtgggtg agagttggac 420

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catcaattct aatctacaaa aggaaattca tgatttcact ctgacgccta ggatctagcc 480
aaggetggtc tgcagtatca gatgtccaaa ctcatctact attagccata ttttgtgagt 540
cgtttgtcta aactttgtca aaatgccttt gccatgattt tgttgctatc tggatttcaa 600
acatggacag ttaggaagat gtgcattgaa gtaggaaaat tttgttcagc atctgctgtt 660
at ttat tttttt taccacttca aaaatggcca ctgtcttttt aacaaacacc aacgacaaca 720
acacacaaaa caaaaaaaaa caccctgcgg cttaccctgg ccctcctttt ccctgttgaa 780
ttgtttcccc cccaatcac 799

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<210> 102
<211> 956
<212> DNA
<213> Homo sapien

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```

<400> 102
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ggggagaaaa accccaccat caacacaaaa gaaggctata aagactgtgc accttttaac 120
aagtcaattt gtagtcagtc cctgggcctg tctttttttt tttttaattt tgaagctacc 180
tgaggtttag aattccttca gcctagctg cttttattct gctttttatt taaacaaaaa 240
gagggggagg atctgaagga aactagtttt ctgtacaaag gctttgaggt ccatggacta 300
tacttgtccc atttatcatc ccaggtggtg ctttgaccct gccataccct ggctattaag 360
ataaaaagat ttgtggacat taaaattatg aatatgtcag taataatcca gcacacattg 420
aaatattgac acagattacc ataatttgtg caacatctta taaacaatgt catttccata 480
gtagtotaag gcttcaccag cctggccac tgtatctaga ctttaggttc attttaataa 540
ttatgctttc cttctctgta tcatttgga agttgataaa tatcacttcc ttagatacct 600
tcattcagtg atatatctgg cttttacaat taaattggaa aaggtaagtt tctctttggt 660
gggttgagag ttggaccatc aattcta atc taaaaagga aattcatgat ttcactctga 720
cgcttaggat ctagccaagg ctggtctgca gtatcagatg tccaaactca tctactatta 780
gccatatttt gtgagtcgtt tgtctaaact ttgtcaaaaa tgcctttgcc atgattttgt 840
tgctatctgg atttcaaaca tggacagtta ggaagatgtg cattgaagta ggaaaatttt 900
gttcagattt gctgttattt attttttaaa taaaaaatgg aaatgtaaaa aaaaaa 956

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```

<210> 103
<211> 488
<212> DNA
<213> Homo sapien

```

<400> 103
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 aatgttgctc tagatgctgt cgagcggcgc agtgtgatgg ataacttgct cttagaataa 120
 gggtaaaaag taaattaaca agtaagtaaa gtatagatag atgttgccac agacatacag 180
 gaaaaataaa aagaaaaatt aaaccagaaa aataacacaa aaacattaaa gaggagctga 240
 aacaaatcaa aaaaagaaaag aactaatata gcctagtttt caaagaaaaa cattctaaaa 300
 gttaaactt tcagaacata gaatactatc taagtttacc atacttcaaa aatctatcta 360
 aataaatatt gacactatat tacattaaca caacaaacag ctattttcta agtactagcc 420
 aagtatccca tggaaggcaa acgaccctaa gtagttcata ttttacagcc cttgaactta 480
 taaagctt 488

<210> 104
 <211> 386
 <212> DNA
 <213> Homo sapien

<400> 104
 aacccctggc caggcccagc tgccacaccc tttctgggag aagcatggcc tacagaatga 60
 agagggggac caggaacccc tgtgggagag gcttagacct gaagcagtgc cactctggc 120
 tcctcctgcc ttggctgact gggttcctgg accatgtgca tttcactggg ccattgggac 180
 tacatctcct tgcaccccca gctggtctga tcctgcccag ggccccctcc tcctgctca 240
 tggctctcag gtggcctgat catggaaagt aaggagttag gcattacctt ctgggagtg 300
 accctgactc catcccccta ttgccaccct aaccaatcat gcaaacttct ccctccctgg 360
 ggtaattcaa cagttaaaag aagctt 386

<210> 105
 <211> 1713
 <212> DNA
 <213> Homo sapien

<400> 105
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 cgcacccgta gaccagaccc caaggacct ggccaccatg ggccagagag cattaccttc 180
 atctctggct ctgctgagcc ggcccttgag tccccacct gctgctgct ctggcgaccc 240
 tgggtgtggg agtggtgccg ggctgccttc tgcctccgcc gctgccggga ttgcctccag 300
 cgctgtggag cctgtgtgcg gggatgcagc ccctgcctgt ctactgagga ctccactgag 360

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gggactgctg aagccaactg ggccaaggag cacaatggag tgccccccag ccctgatcgt 420
gcacccccca gccggcgga tggccagcgg ctcaagtcaa ccatgggcag cagcttcagc 480
taccgccgatg ttaagctcaa aggcacccct gtgtatccct acccgagggc cacctcccca 540
gcccctgatg cggactcctg ctgcaaggag ccaactggccg atccccacc catgcgacac 600
agcctgcccc gcacctttgc cagtagtcct cgtggctccg aggagtacta ttctttccat 660
gagtcggacc tggacctgcc ggagatgggc agtggctcca tgctgagccg agaaattgat 720
gtgctcatct tcaagaagct gacagagctg ttcagcgta accagatcga tgagctggcc 780
aagtgcacat cagacactgt gttcctggag aagaccagta agatctcgga ccttatcagc 840
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tcaacagtta aaagaagctt atcttaaatg tattgtattg ggggtgggc agggccact 1620
ctatgttatg ttaaggagtt ggttctggtt cttggctgat gttctgtatc ttaacatgac 1680
cacagtttgt aagtacctcg gccgcgacca cgc 1713

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<210> 106
<211> 797
<212> DNA
<213> Homo sapien

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```

<400> 106
aaaaaaaaacc acaacaaga gaggattgat tgataatatg gggcatgctt aatctaata 60
tgctcgagcg gcgcagtagt gatggatcga gcggcgccgg gcaggtaacct aacatatagt 120
agacagtgga gagtgggtct ctttcgttgt ctcaggggca gacagatggg gtgctggagt 180

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cctctatcaa agagtcagag ctctatccca gatgtgtaat gaacgtgggc acagacatat 240
tgtcccatta ccattttacct tccctataac cactgtgcct ccagccttgt agaatagaca 300
cataggagcg cagcaatacg tctaaaaata ggagtgagag agggcagggc atgcccgttc 360
ttgtggtaga agaaaagaat gtcaaagaaa gcagctggga ctaatgaact ttacattagc 420
catattccat tatttcagct taagtcaaat gtcggtcctc atgaggcaac tggctttgac 480
aggagctacg ctaatgtgcc acttaccaac cttaatttc tgggtaaaag cagaaagaga 540
aaaactaatg gatttttcat tttccagaag agacaagaat caactacact agtagtctgt 600
cagaacaaaa gaaaacctgc atccaattac aagaattatt actgtctctt taataaataa 660
ccacattatt taggctgtca aaacacaaaa aaaacaaaaa aacaaaaaca ctcgcgggggt 720
aactacagga gcacaacgtt cccctcgtgt ttaaactttt ttttcgcgcc aaattcccac 780
cacattagaa caaaggg 797

```

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<210> 107
<211> 1386
<212> DNA
<213> Homo sapien

```

```

<400> 107
actgtactcc agcctgcaac agagtgagac actgtcacac aaaaaagaaa gaaatatcac 60
aatatgtcac aataggccgg gcgcagtggc tcacacctgc agtcccaaag tgctgggagt 120
ataggtgggtg agccaccacg cctggcctaa atgaagtacc acatgaccga ccgaccgacc 180
tggggaacat agcaagaccc catctctaca aaaatgtaaa aaataaaaat tagccgggtg 240
tagtgggtaca tgcctgtaat cctagatact cgggaggcta aggcagaagg atcacttgag 300
cccaggagtt cgaggctaca gtgagctgtg atcgtgccac tgcactccat cctgggtggc 360
agagtgaggc cctgtctcaa aataaataat ccagtcccc ccaagaaagg aatgaagtgc 420
tataatgaga aaaatcctag tacctaacat atagtagaca gtggagagtg gttctctttc 480
gtttctcagg ggcagacaga tgggggtgctg gagtcctcta tcaaagagtc agagctctat 540
cccagatgtg taatgaacgt ggtcacagac atattgtccc attaccattt acctcccta 600
taaccactgt gcctccagcc ttgtagaata gacacatagg agcgagcaa tacgtctaaa 660
aataggagtg agagagggca gggcatgccc gttcttgtgg tagaagaaaa gaatgtcaaa 720
gaaagcagct gggactaatg aactttacat tagccatatt ccattatttc agcttaagtc 780
aaatgtcggg cctcatgagg caactggctt tgacaggagc tacgctaatt accacttacc 840
aacctttaat ttctgggtaa aagcaaaaga gaaaaactaa tggatttttc attttccaga 900

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gagacaagaa taaaataata gtagtctgta gaaaaaagaa aacctgcac aattacaaga 960
 attattaatg tatctttaat aaataaccac attatttagc tgtttaattt cctaaaaaaa 1020
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1080
 aaaaaaaaaa aaaaaaaaaa aaacaaaaaa aaggagggggg ggggggagag aaaaagagcc 1140
 gaggggggag cacagagcgg gccgccgcgc acatatgaaa aaagcgaccc agaagaagaa 1200
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 agaaaggaaa taactacagg accaacacgg gacaaaccaa aagcaaataa acaaagaaaa 1320
 taagacagac acaagatgcc aacgagctaa cgcccgagca atggaaacag gtaaacaaca 1380
 taaagc 1386

<210> 108
 <211> 749
 <212> DNA
 <213> Homo sapien

<400> 108
 aaagatgatc atcatatggg caatgggcct ctagatgctg ctcgagcggc gcagtgtgat 60
 ggatgcgtgg tcgcggcgag gtactttctc caaaattagc atgcagctat ttaataggga 120
 atctagattt caccaagatt caaatcaaag caacatttaa aggaataaga cctgttcact 180
 aagcattttc aaggggggtc taaagcattc aagtgcctaa aagccataaa aaatgacttc 240
 ttaattcctg cctttagtgt caacttttaa gttaatacag gtttcaattg tggcattaga 300
 aaaaaaaaaa accttgtgat gctatggttg ggggtagtta gggagagact acttgaaatt 360
 gtgtgcccct attttcttctc tgatcctaaa tcatttggtt ttataaatca gctatagcat 420
 ctttctagaa ttaatcctga atatgttgaa tgtaaaaata gagaagttgg tatatacaca 480
 taattaaaaa tcaacccttc tgggcaagat ttcactttga aggtgtctgt ttttaaggga 540
 agggctaaaa ctttggtctg atattgtgat aaaacttgaa ctctaaaaaa aaaaacaaaa 600
 aaaaacaaaa aaaaaaaggc tgggggggac ccaggggggc aaacgggtgg tccccgggtg 660
 tggaaatttg tgtttcccg cccccaattc cccccaattt tttccacaac aaaaggcagc 720
 aaaaacaaac aaacaccacc acacaaaaa 749

<210> 109
 <211> 623
 <212> DNA
 <213> Homo sapien

<400> 109

99

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tcgcgccga ggtacttaat aatgactgaa tttcatgttc ctacagtcac acatattcat      60
tagaagtttt atgttggttg tctgatctga ttcttcttgt tgtgggtgga acggcactga     120
gagaagtata gttttttaa cttgaacatg ttcagtagtt acattgcctt agaaaacca      180
gacacatagc agtggaaatg aaagaaatgg catcagaagt gacttaattt agcaattgtg     240
attcctcttg taaaacaaaa caaaaaaaca atgccatatt tttggagaaa agttggcaat     300
ataggggttt cggtgtctgt ttcacaagaa gactcatttg ttcttttggg ggaaccagtg     360
ccttacagat ttgtatatac tgtaattatt caggactagg gaacaaacaa ttgtattgta     420
tttgttacag attgtatatg gctttgtttt aacattcccc taaataaaat ggcttcattc     480
tcccccttga aaaaaacatg actgttatgt tataaaaaaa acaaaacaaa aaacaaaaaa     540
aaaacaagcc ggggagaaaa caaggaaca aagacgggcc cgcgggggaa aaaggtaacc     600
cagggacca aattccacca aaa                                           623

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```

<210> 110
<211> 1944
<212> DNA
<213> Homo sapien

```

```

<400> 110
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ttaggaaaca agtagaactg taatcagaac gctgcttcaa ttgatattaa aaataacctc     120
aataataatg taaaggttcc tttctcttgt gtcagttata ttcttaggga tagcctagaa     180
ggaatatatg gttagaacta agtgtgacta atcatctgag ccttgaagag aaacttcagt     240
gcctctaaac agatcatcta caaaacaaca ggtaaacatt tatgccagtt aagtgggtca     300
tgttttttgt tcttgggttt ttcctaaatt taagtgaggt tgggcttacc ttgtagataa     360
aattatgttt tcttttttgt aaatacttga atgtggataa cgtcaaatca gaatattttg     420
tgaggaggtg atgatttgaa attaagctag atttctaggg aggtgttggt tccaatgaag     480
gatgggaaga aattaaaata gtcttcaaac ttcttcctta ttatatattg ttgctttgga     540
aaagattggt cctatcctca atctaattta ttcactatta atattttaaa aacattcctg     600
agatacttaa aaagaccac ttagcgatta tagttgctca atgaaacaag aatttattta     660
tgcatagatt tttctctgta tcttaccaaa atccacttta cttagataac actaaattgt     720
tcttaaagac tactcatttc ccaataatcc tttatgattt caaaatttct agtggctcag     780
aagtgaattt tattttattt gtctttcact tgaataaatg agaaccaga aattaataat     840
gttgtttatt gcttactgtc aggactattt caaagactaa gaagagtttc ttctaacccc     900

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100

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tccctctcaa aggaatccta aattattagt tgtagataa gttttgtatg ctaagatatt 960
cagggtttata gtttatgtat gtgtgtatat atataaatat atatgtatat ataaatatta 1020
tgttcagttt ggagtcctggc acaactccat tatgtggatt agagagtaag atattatgga 1080
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acacatagca gtggaaatga aagaaatggc atcagaagtg acttaattta gcaattgtga 1560
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ccttacagat tttgtatata ctgtaattat tcaggactag ggaacaaaca attgtattgt 1740
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ctcccccttg aaaaaaacat gactgttatg ttataaaaaa aacaaaacaa aaaaaacaaa 1860
aaaaacaagc cggggagaaa acaagggaac aaagacgggc ccgcggggga aaaaggtaac 1920
ccagggacca aaattccacc aaaa 1944

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```

<210> 111
<211> 692
<212> DNA
<213> Homo sapien

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101

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<211> 8144
<212> DNA
<213> Homo sapien

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102

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104

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105

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<210> 113
<211> 521
<212> DNA
<213> Homo sapien

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<400> 113
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106

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 <211> 386
 <212> DNA
 <213> Homo sapien

<400> 114
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<210> 115
 <211> 765
 <212> DNA
 <213> Homo sapien

<400> 115
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107

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<210> 116
<211> 356
<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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108

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 <211> 517
 <212> DNA
 <213> Homo sapien

<400> 118
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 <211> 730
 <212> DNA
 <213> Homo sapien

<400> 119
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 acataagttt atcgttatga gatatgttct ttattttgaa gtgcttattg tccattttac 480
 attgggtcat ctgttattga attgtaaaca ttccttgaat atttaaatat gagtgcttgg 540
 tcagttttgg tcacaaatat cctcgttttt tcaatttttg ccctttttatt attctgaaaa 600

109

tgccaagtga	ttaaaattaa	ttttactatt	gtcaaaaaaa	aaaaacaaaa	aaaaaaaaag	660
ccgggggtaa	ccgggggacaa	agcgggtccc	gggggactgg	tttcccgcca	acattccaca	720
ttgacgaaac						730

<210> 120
 <211> 1364
 <212> DNA
 <213> Homo sapien

<400> 120	
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tttgtgggtt	
atatgcatca	
gaaagagtaa	
gacttaattt	
tgtgtggaac	120
aaataccctg	
gtgtagcatg	
tttcattaga	
atttgtttat	
agagatat	
ccatagaaaa	180
gttatttttt	
attagtaaag	
aatgctttgt	
atttcctttg	
tggtctctaa	
gtaccctttt	240
ttggttatta	
tacctttatc	
cataagtatc	
tttaaattatt	
acaaaaatta	
catattcttt	300
taaatatttt	
aaagatttat	
tatattcatt	
taggttttaa	
tccactttta	
atTTTTtaga	360
tgaaaaagtaa	
gagaaaagta	
tataaatcat	
gagcacaat	
tgaactaacc	
aaggtaacaa	420
tcaatctgct	
caagaaattg	
agcatcacca	
ccacctctc	
ctgcaactgc	
caaatcagca	480
ccccagtact	
ccaaagcaaa	
tggtactcac	
tacactgact	
tctaacacaa	
tagacttggt	540
ttgtctggtt	
tcaactatac	
aaaaatgaat	
catagagtat	
gtgttggttt	
gtatctggct	600
ccttttcaacta	
aaatTTTggg	
ttataaaaatt	
catccatgtg	
gttgaacaca	
gtttagatt	660
gttcatttta	
attgTTTTac	
agtatttatt	
gtgtgactaa	
aacactactt	
atTTattcta	720
taattgacag	
actTTgggtt	
gctTTtgctt	
tgggagtata	
aacattTTta	
tatctatgct	780
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gttcatgaat	
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taattacttg	
agtgtgaaat	
tgTTatgtta	840
tgcgatatat	
agtagtcaaa	
tatagaagat	
aatgcaaaac	
aatttaaagt	
gattgtagca	900
gtttgctgta	
ttctacagca	
gcagattgta	
gcagattact	
gtattctaca	
gcagcagcat	960
gtgagattgc	
cagttgctca	
aattcgtgcc	
aatacttggt	
atTTTTtatt	
ttttaatttt	1020
agacattctg	
gagagtgtgt	
agtaattttt	
catcttgga	
aattacatta	
aattagtatc	1080
catttctcta	
atTTtgataa	
cattttcata	
agtttattgt	
tattagatat	
tttctttatt	1140
ttgaagtgt	
tattgtccat	
tttacattgg	
gtcatctgtt	
attgaattgt	
aaacattcct	1200
tgaatattta	
aatatgagt	
cttggtcagt	
ttttgtcaca	
aatatcctct	
tttttcaact	1260
tttgcccttt	
tattattctg	
aaaatgccaa	
ttgattaaaa	
tttaattttac	
tattgtcaat	1320
aaaaaaaaaac	
aaaaaaaaaaa	
aaggccgggg	
gtaaccgggg	
acaaagcggg	
ccccggggga	1364
ctggtttccc	
gccaacattc	
cacattgacg	
aaac	

110

<210> 121
 <211> 578
 <212> DNA
 <213> Homo sapien

<400> 121
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 gtgggtcgcg cgaggtacca cctgttcatt tggggaactg tgggaaacgg agccaacgga 120
 cctaagtgcc ctttgacagt gagtttcata ccatttcagt agtgatattc tttcttaatc 180
 tgaataaacc agtatgatac tctcagacac agaagaataa agggagcgag tcattaacgt 240
 tttcttttta aacctttatg atgacttcct tatgaattac tgaacgaaca ctggaatggg 300
 actcaggat cctgaggaca tctctcaact ctggccttag ttccccctct gtaaaattag 360
 ggtgccaact aaatgatcta caaggtcct tccagcgccg ccattctgta attacatcat 420
 gtgtaactgt attaaacata cacaagtgc tgccaggcat gggaatgtaa cttccgagta 480
 aatgctttgg tttgttcaga atacactatg aacttctttc caaagacggg ttgtggtaaa 540
 tagtggatat tttgattata agaaatagag tttccttg 578

<210> 122
 <211> 1138
 <212> DNA
 <213> Homo sapien

<400> 122
 aagaaattcg gcacgaggaa agtgctggga ttacaagcat gagcccagcg cctggctgta 60
 tctttcattt tacccaagtc actttaccca agtaagtaat taggggaaag cctgagtctt 120
 gtaccacctg ttcatttggg gaactgtggg aaacggagcc aacggaccta agtgcccttt 180
 gacagtgagt ttcataccat ttcagtagtg tatttctttc ttaatctgaa taaaccagaa 240
 tgatactctc agcacagaag aataaagggg gcgagtcatt aacgttttct ttttaaacct 300
 ttatgatgac ttccttatga attactgaac gaacactgga atgggactca ggtatcctga 360
 ggacatctct caactctggc cttagtctcc cctctgtaaa attaggggtgc caactaaatg 420
 atctacaagg tcccttccag cgccgccatt ctgtaattac atcatgtgta actgtattaa 480
 acatacacia gtgactgcca ggcattggga tgtaacttcc gagtaaagtc tttggtttgt 540
 tcagaatata ctatgaactt ctttccaaag acgggttgtg gtaaatagtg gatattttga 600
 ttataagaaa tagagtttcc ttgaagcttt agctggagat acagcaatag tgtggtgttc 660
 ctacaaatat cacagtgtat tcaaacatat tttctatca aaaatcattt ttgtaaaagc 720
 tgtgtgtttt tatccaactt gtgataataa atgttcttta ttttagaata aaaaaaaaaa 780

111

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aaaaaaaa aaagaaaaaa aaaggaaata aaaaaaaaaa acaggagaca aagacaacgg      840
cggcacgcaa caaccacatc gcggaaggcg acaagcgaac aaccagccc gagctcgtga      900
aggcgagcca acatgaagga gcgcactatc caagacaggt agctgacata acagaagaga      960
acaaaaacaa gagacaagta gaacaaaaac aaagagaaga caggacacac gagaaaagca     1020
gggtgtaatca gacgaacgac gcgacaaaaca gagagacgtg caagcataaa atagcaacaa     1080
ccaagagaca gcgacggaca cacgaagcaa gacgagcgac gccgagcaca gcagggat      1138

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<210> 123
<211> 963
<212> DNA
<213> Homo sapien

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<400> 123
tggaagaagg aagggaagag aagaacagag agaggagagc aggagaggag aaagaggaga      60
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ggatcgtggc gcggccgagg tcttaactga taaacagaat atttagaaag gcgagacttg     180
ggccttacca ttgggtttaa atcatagga cctagggcga gggttcaggg cttctctgga     240
gcagatattg tcaagttcat ggccttaggt agcatgtatc tggctttaac tctgattgta     300
gcaaaagtgc tgagaggagc tgagccctgt tgtggcccat taaagaacag ggtcctcagg     360
ccctgaccgc ttctgtcca catgccccct ccccatcccc agcccagccg aggggaatccc     420
gtgggttgct tacctaccta taagggtggt tataagctgc tgtcctggcc actgcattca     480
aattccaatg tgtacttcat agtgtacaaa tttatatcat tgtgaggtct tttgtctttt     540
attttcttat tctaaaaacg ggaaatatgg cggtactcta ctttaaaactt ccaaaaatac     600
cggttattat atgggaaccg ccaaaaaaaaa aaaacaaaca gaaagacaaa cgaggggggat     660
acacaccacg ggcgaaaaag aatacacaca gcgggggaaaa aggggaaaca cagcacaaaa     720
accacacaga caagcgcaac aagaccgcgc aacaggacac gacgcaacac gcacgaggcc     780
gagagcgtta tggaacgggg cagcggggac cgtagaggca gggagcttgc atcaggggag     840
gagagcggac tggagggggg gcggagaagc aggggataga aacagagagc gagaaggagg     900
aaaatgcgcc gggggggagaa agaggcgacg tagagagggg accgagggag aaacgcagca     960
acc                                                                 963

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<210> 124
<211> 986
<212> DNA
<213> Homo sapien

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112

<400> 124
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 tcgccccgggc aggtaacgta gaatgttcat tgatcatgca ttttctgtc attgaagtgt 120
 atcttttatg tttttaaatg cattcatttt acacttgtgg agtttatcat gactttaaga 180
 ggtagaaatg aaaaatgaaa attaaagcta aagccttttt atctattaat gcagatatat 240
 tagaataaga atattttggg tttgtgttta tttttaatg aatttatgtt tacttgatat 300
 ggaaaattac gctttatagg tggaaaagta gcaataaag attaagtaaa agtaagtga 360
 aatgatgggg aatatagtat tggaatttta ttagctagtt aaaacaataa gtatcatcta 420
 atttgggtgt ttattttgca gatgagaaaa cagacctaga accgtggcat gttttgcctg 480
 aaacatacag tgagttagag acagggccta agatagcttc tagcatcaga tcaatcccaa 540
 gaatccatca gcaacctcag accaacccaa gaagataatt taaatctata ctgcttattg 600
 gtcaatatat ttggttctag tattaataaa gaaacaatgt tattaataa gcatacatag 660
 tagtaaaata aaaataccaa aagtgtgttg atttatagct gtttgagatg ataaaagtga 720
 agcaaagcct gttaaactcat tggaagactt ggaaacagtt attttaaagt aaacaattac 780
 atgtactaaa aaaaaaaaaa acaacaaaac aaaaaaaaag cgctggggga cccctggggc 840
 aaggcgggtc cccgggggag aaattggttt ccccgcccaa aatcccccc aacagtgcgg 900
 agacaagagg gcacagacga cagagcgacg aaggaaacac aaagagcaag cgaaacagaa 960
 gagcacaacc agaggcagac aaccag 986

<210> 125
 <211> 986
 <212> DNA
 <213> Homo sapien

<400> 125
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 cgcagtgtga tggatgcggc gcccgggcag gtactttgtc cctgattaaa taatgtgacg 120
 gatagcaatg catcaagtgt ttattatgaa aagagtggaa aagtatatag cttttagcaa 180
 aagggtgttg cccattctaa gaagatgagc gaatatatag aagatacgtg tgggcatttc 240
 ttctgttag gtggagctgt atgctgttga cgtttctccc catactcttc cactctgtt 300
 ttctcccat tatttgaata aagtgactgc tgaagatgac ttggaatcct tatccactta 360
 gatttaatgt ttagagaaaa acctgtaggt ggaaagtaag actccttccc tgaattgtca 420
 gtttagagca acttgagaga agagtagaca aaaaataaaa tgcacataga aaaagagaaa 480

113

aagggcacaa agggattggc ccaatattga ttcttttttt ataaaacctg cctttggctt 540
agaaggaatg actctagcta caataatata cagtatcggt caagcagggt cccttggttg 600
ttgcattaaa tgtaatccac ctttaggtat cttagaacca cagaacaaac actgtgtttg 660
atctagtagg tttctatttt tcctttctct ttacaatgca cataatactt tcctgtattt 720
atatcataac gtgtatagtg taaaatgtga atgacttttt tcgtgaatga aaatctaaaa 780
tctttgtaac tttttatata tgcttttggt tcaccaaaga aacctaaaat ccttctttta 840
aaacaaaaga aacaaacgac aaaaaaaaaa aaacaaggct gggggtagcc tggggccaaag 900
gcgggtccccg ggggaatttg gtccccgcc ccattcccaa cctccgccaa gaacaaggga 960
acagaagaaa aaaaaaaaaa aaaaac 986

<210> 126
<211> 556
<212> DNA
<213> Homo sapien

<400> 126
acctattcac cattccaacg tgaagaagct ctgcatgtag gaaagaataa ttaacacact 60
tatagtctac tgcccatgta aggatcagct ccggctaaga ggccaaagat gggtgacatc 120
gtcatgctct gccttttatt ttttctttct taccactta gcttcctaata tggaggaagg 180
aggcgtggta aaggatatatg aagactatgg tttaattaga ccagaaaaca ctgtcataat 240
ctctgggcgt cagtcagaat gtccagtttt gtctttgggc caagataagg gcagtgggat 300
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ccagacgaga cataaagacc ctgttgggaa tgacattgaa ctctcaaagt caagatttct 480
tacacaaatc tatcagctgg agaataatga gaggcagctg tggatatatgt gtgcaaataa 540
ggacattatg aagctt 556

<210> 127
<211> 1327
<212> DNA
<213> Homo sapien

<400> 127
ggaagacctg attgggaata gtcgaaagcc ttgatatgtg caaagaaaga accatttgat 60
caaccagtt cttaatacag gatactaact taaaatatag actcaagtta tacgataatt 120
caaacattta ttgtatttat actattctat atgtactttt ccaggaacca ggaatacaaa 180
actgacatgt tctctgtaca gaggctcaga ctagtagaga acagttagggt acgccgttaa 240

114

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ttataaacta atatgtatca tcaattatgg gtttttatgg gggtttggca ggtggaaggg 300
accagggaga gatgatgagt gatgatgggt atgtagtctt taggaggatg caattataac 360
attgctcttc ctttcacgca ccacatgatt tagcaagtac ttcattattg ctccaccatt 420
aacatggcca atggcttctg gatactcaca gtccaggcac agtttctcct gaagattttt 480
tacctctccc atctttaaga aattgtctgg atgtccatga aagatgctga cacttgattt 540
aattcattaa aaaacaccac cccctccctg aaataaacta aaaagtaatg aattcataga 600
aaaaaatttc accaagattg aaactagaga atatacctag acttgcaact tgagctttga 660
gaaatgtgta cctattcacc attccaacgt gaagaagctc tgcagtagga aaaataatta 720
acacacttat agtctactgc ccatgtaagg atcagctccg gctaagaggc caaagatggg 780
tgacatcggt atgctctgcc tttatttttt ctttcttacc cacttagctt cctaattgga 840
ggaaggaggc gtggttaaagg tatatgaaga ctatggttta attagaccag aaaacactgt 900
cataatctct ggggtcatca gaatgtccag ttttgtcttt gggccaagat aagggcagtg 960
ggattttatga tgtgttgttt atagtctgaa actactctgg tgatcaccag ggtcagtttc 1020
tttaatgatg gtttccaact ggcctaatac attaagtaag actggctgat aacatgacca 1080
gacagacata aagaccctgt tgggaatgac attgaactct caaagtcaag atttcttaca 1140
caaatctatc agctggagaa aatgaaggca gtgtggtata tgtgtgcaaa taaggacatt 1200
atgaagctta aatatggaat gtctcttgga ccccgatgt catctgtatt ctctttttct 1260
tcttgtacta taccctttgc ctgtaaataa aagggtttatt tgaaaaaaaa aaaaaaaaaa 1320
gatcggc 1327

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<210> 128
<211> 472
<212> DNA
<213> Homo sapien

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<400> 128
accctttatt aagctgtgag cttcttgagg gcaaggactg caattcatta atcattttgg 60
agaaaagtga ataattctga agaattcggg ggttcatgag cttgcctggg atttgtttct 120
ctatggctta tcatctaagt gagataacag atagtagata attgataaat ttaatctggt 180
acctaattac tgagaggatt cgattcttgc tttatgttat tactgaaaca gactgccag 240
taatcttctc tagagagcaa ttaggtttgc aatgagttat tttattgaga atgctacttg 300
gaattaaatg tttatagcac tatcttgata taatttaaat ataatttaaa tgtgctgaag 360
tatcttcatt cagataactt gttaccctt aacaaaaggc tgcttgagta ttgtttctct 420

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cccatttggc aaacaccaga tgcagtgatt aataaaggctc attatgctac tt 472

<210> 129
<211> 1040
<212> DNA
<213> Homo sapien

<400> 129
ggggatttag gttatttttc actttaaacg ggctattaac ttcacgtgag aaaaaaactg 60
tagaaacgtt aactcctgta gaatgatgac tatctgtggg gtagtaagat catacaactt 120
ctctacttgt tactgtgagt tgcttaataa atggcagtac aagtgtcaaa tccataatta 180
gtcaatatca agagctgcat tttggattgc atgtactgtc ccaaataat gttgtgcaag 240
ttactttgta tcatgttaat ggagaaaaga gtggatatta tgaaatcagc aatataaatc 300
aaatgtatat gtggctctgc aatgtaattg aagggtactca gtgttctcag acactcatgc 360
aatatcttgt gttgctttct cagatttttt aggtgtatca taggggatag ctgggaactg 420
gtagagcaga ggtactaagt tccacctgga aatgcttttag agtagctctt tgaatatgtc 480
ttactttatt atcttacagc gtatgtgtat atgattatct tctagagggt cgtacccttt 540
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tgaataattc tgaagaattc ggtgggtcat gagcttgccg ggtatttggt tctctatggc 660
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tactgagagg attcgattct tgctttatgt tattactgaa acagactgcc cagtaatctt 780
ctctagagag caattagggt tgcaatgagt tattttattg agaatgctac ttggaattaa 840
atgtttatag cactatcttg atataattta aatataatct aaatgtgctg aagtatcttc 900
attcagataa cttgttacct cctaacaaaa ggctgcttga gtattgtttc tctcccatct 960
ggcaaacacc agatgcagtg attaataaag gtcattatgc tacttaaaaa aaataaaaaa 1020
aaaaaaaaaa aaaggcggcc 1040

<210> 130
<211> 242
<212> DNA
<213> Homo sapien

<400> 130
agtttttattc ttttcttgac tttttctcct gaacacttat gtcttagcaa gtgggtcaaca 60
tgaggatttg aacgcctaatt tgttggtaaa tgggtgaggg atgacaaaaa tattaatatc 120
cactgtttac catcacgtta tttgaaacaa aagtgacat gtatactatc ttgcttgaag 180

116

aagtctttga cagaaaaagc aatatcatgt catttataaa ttttcttggt ctaaagaaag 240
ca 242

<210> 131
<211> 1689
<212> DNA
<213> Homo sapien

<400> 131
gtttgcaggc cagatggctt ctgtggcagc tactcagctc tgcaatttca gtgtgaaaga 60
agccatagac agtacttgaa tgaaggactg tggctggatt ggcccttttag tttgaccccc 120
tacattaggc cccaaatttt cttaccctga ggtgctgata tctgtatgga tgagtatttt 180
gtcactaaag ttatgagttg tgccataaag ttaaaactgt tgactgtatt atgtaatgat 240
cagtatttca gttgggaaga tatttttagag tctagataat tatgtttgta tattgaaaaa 300
atggtggcca gtttttaagt tccttaatag aagagaatta tgtctcagca catataacag 360
taatgctaatt ttattgaaac tactgctggt agagcacttc ttattcattg tcttttagtg 420
aaatttatgg cgtaacactt tgtcagagag gaggctatat aattcggagc ggaaattgtc 480
tataagtagg catttatttc atgattgata tgtcacagaa atcatggtag taaatcacat 540
tgctatttga ataccctggt tttgtaagtt tttaaaactc atattctgaa aagatttcat 600
tctcttagtg ttagcttggg agttagattg ccatgattaa actattattt atccttgtgt 660
aatattagtt ttttaacttta acatctgttt ctttttaatc tataatgagc tagttttatg 720
gaaaaatggaa tttcttacta tataaagaat acagagactc attgtattag agaatcaagt 780
cagccagcta aagtatccta ctgttaaate cttaaaccta attttggaaa agagaaaagt 840
aatcaatgta tttaccttac atgttggaaa gaactatggt aggtctgatt catgtgaaga 900
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catcatgtta tttgaaacaa aagtgaccat gtatactatc ttgcttgaag aagtctttga 1140
cagaaaaagc aatatcatgt catttataaa ttttcttggt ctaaagaaag cagttatata 1200
tatatataaa ttatgtaaatt aaaagttatt ttatatcaaa aaaaaaaaaa aaaaaaaaaa 1260
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aagaaaaaaa aaaaaaaaaa agggggggggg 1320
aaaaaaaaaa caggggagaa tataacattt ataaaagcaa aagataaaat gaagagagag 1380
ccagcgtcta tcaaaaaaac agaccgatcg aagaaagaaa cagaacaaag aggttaaaat 1440

117

ctgaggacga gaaccaatth gaccggggat taaaaaagag gacaccaccg cacaagaatt 1500
 cccgcagggg aaataaacta ggagttgtac tacgaaccac cctaataacg cagcaagacg 1560
 tgccgacatt aaacaataag cggcgaaatc tacagggaga agaataacag gtaccgagga 1620
 tacacgatag cagcgagagg agaagagtca acacgacaac gtagaggcag aacacacggc 1680
 acagagaac 1689

<210> 132
 <211> 776
 <212> DNA
 <213> Homo sapien

<400> 132
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 tgtctggaga tagacctga atttaataaa ttttaggcac tataccattt cagtggagaa 120
 gattgttggg aaatttgggg ggatggatat ataaggggga ggaagtcact ggccagtttg 180
 aggtgcttcc attggtctgg gtaactagcc atttcttccct gattgtgcct agtatatccc 240
 agacagtttg tttctatgca gaagaatttt atatgaaatt ttcatttctt tgcaaaaact 300
 tggtccttct ttcagttcat gacatcatcc atgctaaagt ctgagtcac tgcttccatt 360
 tttgttattc cccacatcca gtcttcagct aagtcctgtc agttctacct caagtcttcc 420
 ccgtctttct tcctcaccta tgtaatttca gtagtctctc agcttcactt aagctcttac 480
 tccagcctac tttatacaca atgtagatt catcttactg aaacatagtt ctgaccatgt 540
 attccatgca tgtgttctct ctcccctatt agactgtaag ctcccttatgg gcaggatctg 600
 tgtctgagtc atctttgtat cttgcctagc acctatcaat aaatacttct gtgaatgaaa 660
 aaaaaaaaaa aaaagaaaaa aaaaaagggg ggggggaccc gggggccaagg gggcccgggg 720
 gaatgggttc cggcccaatc cccattcccc ggcgcaaaa aagaaaaaag ggaaag 776

<210> 133
 <211> 2910
 <212> DNA
 <213> Homo sapien

<400> 133
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119

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 <213> Homo sapien

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 <212> DNA
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120

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121

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122

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 <212> DNA
 <213> Homo sapien

<400> 136
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123

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124

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<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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<212> DNA

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125

<213> Homo sapien

<400> 140

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126

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127

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128

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130

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131

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132

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134

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ctgtgtgttt ccttccatct ggattttcat a 271

<210> 148
<211> 1148
<212> DNA
<213> Homo sapien

<400> 148
ggtgaattca ccttattttc agttggtaga gtatggaaaa atgtatcact tatttgaaat 60
acctgaatgg aaaccagcc tctactactg taacttaaca ctgggcagtt acttgttctt 120
cctgagcctc aaattttctt tctctgtaag aatgggaatt aatgccacc tacgggttgc 180
aagtgcctac aggagctggg caagcaacga aggtaagagt thtagagact tccggtaaact 240
ggagcacatg attcctggga agcaggccta gtgtaacaa tttatttttc tagaaaagac 300
agaagtttag agtatatgaa atctaatttt taagtattgg ttggcaacta attgactatc 360
gtctaccata aggttatatg ataattatta gggcaggaga gtgaatgcat cttaatatgc 420
atggcagaac tgtgtgtttc cttccatctg gattttcata aagctttctg atttatcagt 480
aacgatctga aaaatgtact gtggcatgta acatctttta ttcattttat taggcattag 540
aggaagaata ttctgtagtc ctgctttatt ctgccatctt tacctggaaa tccattttta 600
taaaattttt gtaataaaaa ttcacttgat cacttgccctg ctttctttta aacagtgcc 660
agcgtaatgc cccttgataa tttacatata tgtgaacgtg gctgtgatag ctgctgatgt 720

135

tcacacatag gccatcttac atgtaatgat tccatgtttg gacttaaaca gcttcacaca	780
tttattgtac agttaggtgt cacatgcttt tactttttat tttataatct gtatttctgt	840
gaggtagaca ttattggctc catgttatat acattgatag cccggagcta gagattgaac	900
ccaggccatc ctccccactg cctttcatca tcaacacaac caccaccaac agtattttta	960
aagtgttaaa tattggcaga cgtgtcattg ttctgagcac taggactagg gcttatgcgg	1020
ctgtctgagg aattccctgt acaaggaaac atcatatacc aaaaagttac tcatggaagg	1080
agtttgagga tgatgagcta aaagtattac acatggacta ttgtaaaaaa aaaaaaaaaa	1140
gcaagctt	1148

<210> 149
 <211> 1139
 <212> DNA
 <213> Homo sapien

<400> 149	
cgaggtagcc attataatta ctaaactgtg aagtcactat tattagtatc tgaccagcta	60
tacaaaacat catcaatttt acttttgaca caaaaggtag taaaaatcgc aaacgataaa	120
gaagacacta ctcatataaa gtcattgtta ctaatccagc accataattc cagtctcaga	180
acctcccatg cagattggaa agggattatg ggaacgaggt gagtatgtag gacatgtcgg	240
cgctagtaac atcaaattga cggccccata tttgctcgct tcacaagaca aaaaacacag	300
ggctctccca aagtaagcag aagatgacat gacggcatgg agacgaaaaa caaaacgcta	360
gcgcgctaaa tcaatggtca atagctgcaa aaccatctga tgacaactag ggtaacttcc	420
cgtgtcaacc aaaaattcac aaacaagtaa gcactacctg tagaacagac acgaagtcac	480
gcaaacctac actttgagca cgctgacca gagatccgag cactctccc gaccaccaa	540
cacacagcag gccacgcggt agagagaaca agaatacaaa ggacaagcga gtagctgtag	600
aagcgatgag agagagcgta cgtagagatg ggggaggaac accacgtagg agcagaactg	660
ctgcactgcg tgcacacgcg acgcgaacag acgaaactac acgaagacaa aaggaaaagg	720
aaaggatggg accagagggg agagccaagc atgagagaca caccaaaagg caccgcacg	780
ctgcatggcg aagcgagaag aacagcagat aaccacaaaa aaaagcacac acggtgggac	840
atacacacca gagggggagc atcagacaca gggacaaacc actaaagcag gagaacatgg	900
cgcgaaagga ctgaactaaa cagcacaac acgcaacgag cagcgaacag ccatcatag	960
gcgtgacacc cgactacagc aaaagaaacg gagaagttat cgacacaagg gatgacaagg	1020
aaacaggcta atggcccaag gagaggaaca ataagatgga tgagcacagt agggcgaaca	1080

136

agggataacc caagtgaaga aacagtgaag aagaggaatg cacacaataa gaacgcaaa 1139

<210> 150
<211> 267
<212> DNA
<213> Homo sapien

<400> 150
actgtagcag tgagctcaag tggtgggtgt atcagctcaa aacaccatgt gatgccaatc 60
atctccacag gagcaatttg tttaaccaaga atctaagaat taaatcttag aatgtattaa 120
tggttaaattt ctgtgagatt atattgtagt cacgtagaat gtcctgactt gtaggaatac 180
ccactaagga aatcagaaat cacggtagag cgtcagcaat ttactctcaa atgggtcaga 240
gaaagaaagt tctttgtagt aaagctt 267

<210> 151
<211> 300
<212> DNA
<213> Homo sapien

<400> 151
gccgccccggg caggtacttg ttttccatgt gtttgctttt atccactggc attttttagct 60
ccttgaagac atatcatgtg tgagataact tccttcacat ctcccatggt cccatgcaaa 120
atgctaggcc tgtagtagtc aagggtgctca gtaaatattt gtttgggtgg tttgtgagcc 180
ttgctgcaa gtccctgcctt tgggtcgaca tagtatggaa gtatttgaga gagagaacct 240
ttccactccc actgccagga ttttgtattg ccatcgggtg ccaaataaat gctcatattt 300

<210> 152
<211> 956
<212> DNA
<213> Homo sapien

<400> 152
tgccagattg gtttttaata taatcctggt cccccccctg cctagaccct tctgctttct 60
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tcacctggaa cctcattaaa tgggtgatttc ttgctaagct ccagcccagag tggctctctc 180
tcagcttcta attttgtgct ctttctgccc cttttctctg gccttctcag ctctccaccc 240
ccaccactct tgactcaggt ggtgtccttc ttctcaagt cttgacaatt cccgggccct 300
tcagtccttg agcagtctac ttctgtgtct gtcaccacat cttgtctttt cccctcattg 360
catttattgc agtttatata tatgctactt ttacttggtc atttctgtct cccctaccag 420
gctgtaaagt agggcagaaa ccttgtttgt tttattcacc atcatgtacc aagtgtcttg 480

137

cacatagtgg gccttcatta aatgtttgtt gaataaaaga gggaagaagg caagccaacc 540
 ttagctacaa tcctaccttt tgataaaatg ttccttttga caatatacac ggattattat 600
 ttgtactttg tttttccatg tgttttgctt ttatccactg gcatttttag ctccttgaag 660
 acatatcatg tgtgagataa cttccttcac atctcccatg gtccttagca aaatgctagg 720
 cctgtagtag tcaagggtgct caataaatat ttgtttgggt ggtttgtgag ccttgctgcc 780
 aagtcccgcc tttgggtcga catagtatgg aagtatttga gagagagaac ctttccactc 840
 ccactgccag gattttgtat tgccatcggg tgccaaataa atgctcatat ttattactga 900
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaatga gcggcc 956

<210> 153
 <211> 784
 <212> DNA
 <213> Homo sapien

<400> 153
 acctggcaca aagcaaacia taaatattat tgttattgtt gttataattg taaaatgaat 60
 gacttcaaaa acatagtccc agtttgaggg gattttgtga tgcagaatat ctaagtcata 120
 gaaatagaag acaggtggaa taagtatatg ttcagagttt ttagatgtgt tgagtagaga 180
 cggtataaat ggaagcatta aatacaaatg aaaatcacac cagatatccc tgaaattcaa 240
 gcaaagaaag ttcacatcatg attcttgggc agcaagagaa aggactaggg ttatggcaat 300
 gtgtggaaaa gttgaggctt gctaagggtt gagatctgtt ggtagccctg gatcacatgg 360
 ggtcagcacc aggcagtgcc tctgaaagcg gagagaggtc ctggacttcc cttgtgtata 420
 acagttccta gtgtccaaca atgaggaaac ggtgaagcat gggtacaaaa ctgtgacaaa 480
 aatatttaca tctagcactg ttaccactca catgccaaac attggctgca cacgtgcagc 540
 cttatttgta attaacatca aaagactaga tctgaagcct tccataaatg agagaccatt 600
 catatggcat tcctggaaca aaacactgca caggtaacaa ggctctccac tccctgacgg 660
 gttggtgctg aacagtcagg gattgtcttg actagacttc tgatgcttct gcattcttct 720
 tcctcttccc ggaattccaa ataaccaatt cataccattg tatttatgct tcgggtaacc 780
 tagt 784

<210> 154
 <211> 2184
 <212> DNA
 <213> Homo sapien

<220>

138

<221> misc_feature
 <222> (1930)..(1930)
 <223> a, c, g or t

<400> 154
 gaaaaataca ttcccgggtg tagtagttct tcatttcctg tctccaacag aaaattcact 60
 catttttagaa ctagtgtaat tcttgataat aaaataagag ttttgattaa gaacagcata 120
 gagcttcaaa atgcaaagtg aatgattagt aaaattatgt ctcattttat tttttcagca 180
 cccataccac aattaatatt aggctggatt gccatgggaa acattttttg gcattaatgc 240
 agcaacataa tactcacttt aggtattact acatagttga aggatttaac tgaatgtatg 300
 gatcaaatTT atttatttga catattcgaa gctgtggttt aataggaatt tgagaaaggT 360
 gtaagaaata ggataaaaag aaggtcagca ccatgtacca ggaatagctt tactttccat 420
 acatagaaat ataaatttag tggatccta tattacttta gtgtcgtacg ctttgtaaga 480
 cttaaattatt ttattctatt gattccacta ctttggtatg ttaagacatt tctttaaaga 540
 tgaccaacaa tatccttatt ttaggtgccA ctagcagatg taagcgtata cttagttgcc 600
 gttagatgtg acagaatgag ataatttatg taaagcagta gagtacctgg cacaaagcaa 660
 acaataaata ttattgttat tgttggtata attgtaaaat gaatgacttc aaaaacatag 720
 tcccagtttg gagggatttg tgatgcagaa tatctaagtc atagaaatag aagacaggTg 780
 gaataagtat atgttcagag ttttttagatg tgttgagtag agacggtaat aatggaagca 840
 ttaaatacaa atgaaaatca caccagatat ccttgaaatt caagcaaaga aagtTcatca 900
 tgtattcttg ggcagcaaga gaaaggacta gggttatggc aatgtgtgga aaagttgagg 960
 cttgctaagg gttgagatct gttggtagcc ctggatcaca tggggtcagc accaggcagt 1020
 gcctctgaaa gcggagagag gtcctggact tcccttgtgt ataacagttc ctagtgtcca 1080
 acaatgagga aacgggtgaag catgggttaca aaactgtgac aaaaatattt acatctagca 1140
 ctgttaccac tcacatgccA aacattggct gcacacgtgc agccttattt gtaattaaca 1200
 tcaaaaagact agatctgaag ccttccataa atgagaggcc attcatatgg cattcctgga 1260
 acaaaaacact gcacaggTac cagcctctcc actcctgacc gggttggtgc tgaacagtca 1320
 gggattgttc ttgaactaga cttctgatgc ttcttgcaat cttctttcat ctttcctga 1380
 aatacacaaa ataaacaaat acaataacaa atagtaatta aatgactttc aggataacat 1440
 ctagttgttc agacttcacc cttcacaggT gtgtgtgtat gtgtgtttat gtctgtatat 1500
 tgaagcaatt tgaatttatt tactgtatat tttctgagta aaagactgaa atgaactact 1560
 tgggttcagat catggtgtcc attggtgaca ttgtttggag gcataatatt ctttatatgg 1620

139

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aaaatccttt aattccacag ttagttacct cagattcaga atatgaatac tgttttataat 1680
acgcttttgt aggaatgaat tcgaaaggta gttgtcagta aacaaaagca caacaaacta 1740
atctcagagt ctgccctgat ggctgtgata gggacagaaa gctaaaccct actgctgacg 1800
cgccccgcac attggggcgca gaatttccca agaaaacggg gcaaatcacc gccacgggcc 1860
taactctgaa ctctatacgg gccatctcgc ctaaaccact acaaggcacg cacgggaaag 1920
gactctccgn tcgcgactcg caagcctacg gccccgaac gacaggcgca ccacgacacc 1980
accgggcgct ctacgagaca tgatcagcgt caagggcacc tgaaaaaacg atgccccaac 2040
tagtgcgcc cgcaaccagg cagacactaa gcttgatagc acagcgactg caccaagagc 2100
taatcacgca cacaaccaa gacagaaact acccactcta tcactacacg gacgacacta 2160
gaaacaacct gcaattgtta ctgc 2184

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<210> 155
<211> 418
<212> DNA
<213> Homo sapien

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<400> 155
actgtgctta ttaatctact tactaaatth tcacattgac atttttgggg atgatactac 60
catatacgaa atggaaaatg taatatgctc agtgcttctg taaaatgcag caatactggt 120
attactttac atcagtaggc atctttgaca tgagcatata aatattttgt tgactcagca 180
aagggtgacac tttgtggact aaagtatccc attatatata atgttttttg aaatgttgga 240
aattttgggg aattatcaaa tgtatagaag ttgcatgaag gttatagaga ggtgtaactg 300
tttggttaact attacatgga ttccatacta ggcagtgaca actaacatgt tacttcaact 360
aaaagtgtat aatgggttgt ctttttattt atgaaacata acaagtaatt ttacttac 418

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<210> 156
<211> 941
<212> DNA
<213> Homo sapien

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```

<400> 156
tgaggttttt tcttgaacat acagaagtac taaatactgc ttgcagtata atattgatat 60
tggaagctgc agtttccaga ataagtggag taataactaa acagacattt aattttattt 120
caatatctat ggaaaaaaca cttgattaaa tctccctgta ttttatgttg tctctattac 180
agaatcactt gtctgtttgt tgtgtgccac ttactgacaa aactttaaac agtacttgat 240
gccagctctc tactctgtgg ctgcgggacc tgtttctttt aggtacttgt gcttattaat 300

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140

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ctacttacta aattttcaca ttgacatttt tggggatgat actaccatat acgaaatgga 360
aaatgtaata tgctcagtgc ttctgtaaaa tgcagcaata ctggtattac tttacatcag 420
taggcattctt tgacatgagc atataaatat tttgttgact cagcaaaggt gacactttgt 480
gactaaagta tcccattata tataatgttt tttgaaatgt tggaaatttt ggggaattat 540
caaatgtata gaagttgcat gaagggtata gagagggtga actgtttgtt aactattaca 600
tggatttcat actaggcagt gacaactaac atgttacttc aactaaaagt gtataatggg 660
ttgtcttttt atttatgaaa ataaaagtaa ttttacttac aatttcattg agatcttttg 720
tttttcgaca aatattttta tacttactaa gccagtagca gttaaaacag tgcaaaatta 780
ttcttcacag taatgtttta aaatgacaga taaccaggca tgggtggctta cgcctataat 840
cctagcattt taggaggctt gggcaggaag attgcttgag cccaggagtt gagaccagcc 900
tggacaacgt ggtgaaaccc tgtctctgta aaaaaaaaaa a 941

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<210> 157
<211> 740
<212> DNA
<213> Homo sapien

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```

<400> 157
acttaagcaa atactgagta gtgttttaaa ttcagaaata gagcttctat tatgaacaca 60
tgagaatgat ttttttctct taatcattat taaggaaata ttttaatttc atgggtcatat 120
aatgggtgata agtaatacct gattgtttcc ttttctgttc tagtaactca gaggagatac 180
gtgttttatt tgtgatagca aattcctaaa tgaacattag gcaagtggta tcattatcag 240
gccagctgca gcctcttgcc ttgacctgca ttcctagaat ttctttgttg ctgtaattct 300
tgattaagtg accttgactt tcattttgta attttgctaa tcatcagcaa attcacttgc 360
atgacgttac tgccaaatat gaaggcagtt gaattattat gagtgattgt ggcagagggt 420
tgtgccatgg tgaaaacttt gatgtttgtc tgtgttcatt ggatccatct ttttaaatga 480
cattaccatg agtctgttgt caaacctaaa tatcttttgt tgaattttta atgggactct 540
atattgttgt agttcaggtc ttcattgact aagagattga gagaaatctg acataagaaa 600
atattgtttt cactgcagga ataaagagga agtaacagtg aaaaaaaaaa caaaaaaaaa 660
aaaaaaaaaa aaaagggcgg ggggaacagg gcaaaagggg cccgggggga aaatgttccg 720
ggccaaatca caaaaaaaaaa 740

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<210> 158
<211> 1888
<212> DNA

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141

<213> Homo sapien

<400> 158

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aaggatcctt aattaaatta atcccccccc ccgaaccggt cgctaactga aatgatggcg      60
actggaacgc cagagtctca agcgcgggtc ggtcagtccg tgaaggggct tctcacggag      120
aaggtgacca cctgtggtac tgacgtaatc gcgctcacca agcaggtgct gaaagggtcc      180
cggagctccg agctgctagg tcaggcagct cgaaacatgg tactccagga agatgccatc      240
ttgcactcag aagatagttt aaggaagatg gcaataataa caacacatct tcaataccag      300
caagaagcta ttcagaagaa tggtgaacag tcatcggatc tacaggacca gttgaatcat      360
ctgttgaaat agaatgacat gtaagagtgc tgtaggactc ctttgcctaa tgctgaggag      420
taaatacctt acacagctgt cctctggggt tggttttcta ttttcttctc caaaagttaa      480
gtagaaaaag ttctgtgtta gggccgggcg cggtagctca cgcctgtaat ccagcactt      540
tgaggaggccg aggcgggtgg atcacgaggt caggagtctg agaccagcct ggccaagatg      600
gtgaaacccc gtctctacta aaaatacaaa gaattagctg ggcgtgggtg cgggcgcctg      660
taatcccagc tactcgggaa gctgaggcaa gagaatcgct tgaaccagg aggtggagggt      720
tgcagtgagc caagatcgcg ccaactgcact ccagcctggg cgacagagtg agattccatc      780
tccaaaaaaa aaaaaaagaa aaaaaaaaag aaaagttctg tgttgatgta cagtttctcc      840
taagaagaag cgaggtgggt gaattttgga agcacttctt gaatcggatt aacccatgct      900
cttattgaat tttttcatct gctctgttta gtttgatatt aaagcaaaat taagagggtct      960
tagtttttcc tatagaactt ttaatatgtc aaaagctata ttgtctaaat ttcagtactt     1020
aagcaaatac tgagtagtgt tttaaattca gaaatagagc ttctattatg aacacatgag     1080
aatgatTTTT ttctcttaat cattattaag gaaatatttt aatttcatgg tcatataatg     1140
gtgataagta atacctgatt gtttcctttt ctgttctagt aactcagagg agatacgtgt     1200
tttatttgtg atagcaaatt cctaaatgaa cattaggcaa gtggtatcat tatcaggcca     1260
gctgcagcct cttgccttga cctgcattcc tagaatttct ttgttgctgt aattcttgat     1320
taagtgacct tgactttcat tttgtaattt tgctaatacat cagcaaattc acttgcataga     1380
cgttactgcc aaatatgaag gcagttgaat tattatgagt gattgtggca gaggtttgtg     1440
ccatggtgaa aactttgatg tttgtctgtg ttcatggat ccatcttttt aaatgacatt     1500
accatgagtc tgttgtcaaa cctaaatata tttgtttgaa tttaaaatgg gactctatat     1560
tgttgtagtt caggtcttca ttgactaaga gattgagaga aatctgacat aagaaaatat     1620
tgttttcact gcaggaataa agaggaagta acagtgaatc caatatagtt catattgtta     1680

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142

ttgtccaatc atcaagttaa ctaagcatta tcagattacg tttatttctc atacatatgg 1740
 atattaactt aaggtaaaaa agctggatgt gaaggatctg aaaaggcatt aatttatgta 1800
 ctaattctat aaacatgtat taataattgc agtattatta aatacagatg gactcaaaaa 1860
 aaaaaaaaaa aaaaaaaaaa tatgcggc 1888

<210> 159
 <211> 417
 <212> DNA
 <213> Homo sapien

<400> 159
 ccgcccgggc aggtacatac atattctccg ttttgtgctt gcttttgcat cgggtcataa 60
 gggtaaaagc agttagttgt attgtggagt tttgcatggg tgcagttaac aatggatggt 120
 tcatcagctg agtttaattt agtattctct cttcattcta tttggctctg aaataaattc 180
 ttttgcattc atttaaatat taggattgat caggaaatag tgtttgtaat ctacacgttt 240
 atttgagcct ttaaaaatat ttctgaacag agatttaagc tctgtcagta ttttcattta 300
 ctgatagcat ttatatatta aatatggcat tgtatatattc attattatcc ttcataacag 360
 aattataatg agaatatgaa tttgttattt ttcttgttgg tagatgtgaa aatggtg 417

<210> 160
 <211> 1545
 <212> DNA
 <213> Homo sapien

<400> 160
 tccttctctt catgtacatg tctgtgcaca tgcacgcaca aatacatttg taatctcact 60
 cattaccttt acattttggt tatcagtatt taaacagctg aactgcaatc atgacctaga 120
 atatggctta tgttatgggc aggtctgttt gaggactgct tggaagagtc agaggcagag 180
 gaatttgcta ttgtaagcaa aggtgacatt gctgagccat caggaagcgc tgtggctatt 240
 tctggaaaca aagatgtcat attaaaattg gataagttag agttgggtcat gtgcattggt 300
 ggcatactctg ggagaagagg aaaacttggg tgagcaaacc caacaggtct gggaggagat 360
 tacaaatgta tttgtgcgtg catgtgcaca gacatgtaca tgaagagaag gattgtgtgt 420
 gtgtgtctgt ataactcagtt ttcagttatc ttcatgaatg tagggaagcc atgtcagatg 480
 cagatactgg gttgtcagat aaacaagtta tctttcgttt tcaactgcat ggtgtacttt 540
 tttattttcc atagtagatt tacatttcca agttgatatt tcctaaatat ctaattagct 600
 ggaaattggg ggagatcatc ttgtcatgta ctgggtagta ggaggagacc tagacttta 660
 acttgattgt tgataactta tggaatatgt aggttaagttg ctactgaata aatataggca 720

143

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gcttgataaa acacagtggc tcataatcaa gtgctggcta atgtcagcat ctagaacagc 780
ttcttaccta tgacagatgt tgaactgatg ttgagtttaa tgtccgtagt taaagtcaag 840
cagttagcaa ataaataaaa gcaatcagcc tttattctca aagtttggtt tagatacagg 900
cttctttcta aattataaca atgcataaat tatctgaatt ttatgtcttg ttcttcaaat 960
tagggagctg tgttaccctt taatgtgcca agattattta aagcaaaggt cttccttaga 1020
caattattta gccgtaaata tagaaagcta aaaagttaag tacatacata ttctccgttt 1080
tgtgcttgca ttttgcacg gggtcataagg gtaaaagcag ttagttgtat tgtggagttt 1140
tgcattgggtg cagttaacaa tggatgtttc atcagctgag ttttaatttag tattctctct 1200
tcattctatt tatttggtct tgaaataaat tcttttgcac tcatttaaat attaggattg 1260
atcaggaaat agtggttgta atctacacgt ttatttgagc cttactttaa aaatatttct 1320
gaacagagat ttaagctctg tcagtatttt catttactga tagcatttat attttaaata 1380
tggcattgta tatttcatta ttatccttca taacagaatt ataatgagaa tatgaatttg 1440
ttatttttct tggttggtaga tgtgaaatgg tgcttcaaaa aatatatagt ctttctgtaa 1500
aaaaaaaaa aaaaaaaaaa ttctgcggcg caagaattct tgtaa 1545

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<210> 161
<211> 196
<212> DNA
<213> Homo sapien

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<400> 161
acagtatgtg gcccatgggg tgggggaacc ctgctcttaa gggtcccaat tatcagctct 60
gaggtagttc aagcaacaga gcccttgac gatgttcagg gagatagtc cgaatccca 120
agggggccaa ttagattcta atggtgttaa aacacatctt aagggttatt gtaaaaatat 180
ctactctcct aagctt 196

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<210> 162
<211> 1128
<212> DNA
<213> Homo sapien

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<400> 162
tacattgatt gtacacttta tttctattat tattacactg taatatgtaa tgaaagaatc 60
atacactgaa ccataattca gaatcagtgg gagccctgag cttgttttcc tgcaactaga 120
cgggtcccatc tgggggtgat gggagacggg aacagatcat caggaattag attctcataa 180
ggagcgtgaa acctagatcc ctcacgtgca cagttcacga tagggctcat gctcctctga 240

```

144

gaatctactg ctgtgctgag ctgacaggag gtggagctga ggccgtaatg ctcaactcgcc 300
caccacgccc ctccctgctgt gtgacccggg tcctgatgga ccatggacca gtaccagtat 360
gtggcccagg gggtggggaa ccctgctctt aagggttccca attatcagct ctgaggtagt 420
tcaagcaaca gagccccttg acgatgttca gggagatagt ccgatatcc taagggggcc 480
aattagattc taatgggtgtt aaaacacatc ttaattttta ttgtaaaaat atctactctc 540
ctaagcttag aacaatattg agaagaaatg aagtggatgg tggaagccct ggggggtggg 600
ccttcacagt ggggaaggct gtgggtggag agccagggca tcgggtaggt gaaggccagg 660
gatgccactc agcatcctgt agggcccgtg atagcccga gcagcacaga atgatcccaa 720
ggctaagaaa cctctatcta gaatgctctt gaatgttcta gaaccgaggt tctttctttt 780
cttttctttt ctttttcaag acaggaaagt gcttatcaca aagaaccccc gatctcgact 840
ggggaagggg tggcagttga ctctctggcc agcactatgt gtagcacgca tcactagagg 900
tgtgaaggcc ccacagaggc tctggtgtgt ggctttgttt tgaccaaggc gtgcaggcag 960
tggtectacg gcagggctgg ccgcgcctc gcctcagtgc cctcagcgcc ttctgtcttc 1020
tggtctgatt cagagtcccg ggggaaagag actgaccttc tcgacttgcc ctcaggttga 1080
ttacgaagcc tcagagccct tggtcaaggc agtcttgag gacacgac 1128

<210> 163
<211> 870
<212> DNA
<213> Homo sapien

<400> 163
tacgcattta ttttttagact gaacctaaag taggttgttc ttttaacaaa gggtttaatt 60
cgggtgggga atataacata tcaaaatata tgaaccaatg gaaagttact tctagaaaag 120
caaagaaatt gggatatcatt tttgtttctt gggaagctaa ttttgttgaa tgtttagaat 180
tgagcaaaga tgtaaatttt tgaagggcag tttagaaaaa ttaacttgtg aatgaactta 240
agatgtctgt actctatatg tgatgctgtg cagttgtttt tatatggaaa gatgtcaact 300
atagccataa ccaataaaat aaaaactgat gaggcagtga gctttcagca catcttttat 360
acatgaagaa attaatattgt gttgctatgg tggtgaaata tccaagatgt tctgtatcta 420
tgtaaacadg attcctttta taaatgtatt ttattattaa caaacacaaa aaaaaacaa 480
aaaaaaaaag cggggggcgcc accggggcca agcggcccg ggggcagggt ttcccggcca 540
aattccccca ataatgaaac caagagggtca agcaccaaga ctatataaac cgctttatat 600
acgagagtgt atatcatgga catcttagga ggagtgaac aaaggggtgg ggcggaggac 660

145

tcaatgatga agactgcaga cggaggggtga ggagggaggg cagcgcagac aggcgaggcg 720
aaggagagtg agaaagtagt ggagttatca gcgaggagct ttcacgggta ggaggaggga 780
agatagtgtt ggaggaggaa cgacgcgtgg agcgggggtgt aggggaggca agatagtggg 840
gtaggagacc gattgacgag gggcagggga 870

<210> 164
<211> 1186
<212> DNA
<213> Homo sapien

<400> 164
catcacttaa cgccgggatt atacacattc tagaaatgat ggtgggaatg atttgccttt 60
aaaagcctac aaattaaaag gggaaagatg ctaagctaga tgctggtttt ctgtaaagat 120
gaattttagt gcttttaaag gcaaatcatt cccaccatca cttaacgccg ggattataca 180
cattctagaa atgattctga gaggagtgtg tagtatggg cctatctaca ctcacatgat 240
attcttattc acgttttttt taaccataag tggcaaatat tttaaaatat ttgaaaaaca 300
ctccagaatc tagtacgctt tattttttaga ctgaacctaa agtaggttgt tcttttaaca 360
aagggtttta ttcgggtggg gaatataaca tatcaaaata catgaacaaa tggaaagtta 420
cttctagaaa agcaaagaaa ttgggtatca tttttgtttc ttgggaagct aattttgttg 480
aatgttttaga attgagcaaa gatgtaaatt tttgaagggc agtttagaaa aattaacttt 540
gtgaatgaac ttaagatgtc tgtactctat atgtgatgct gtgcagtttg tttttatatg 600
gaaagatgtc aactatagcc ataaccaata aaataaaaac tgatgaggca tgcagctttc 660
agcacatttt ttatacatga agaaattaat tttgggttgc tatgggtgtg aaaaatccaa 720
gatgttttgg atttatgtaa acatgattcc ttttaataaat tgtattttat tattaacaaa 780
cacaaaaaaaa aaacaaaaaaaa aaaaagcggg ggcgccaccg gggccaagcg gcccgggggg 840
cagggtttcc cgcccaaatt cccccaataa tgaaaccaag aggtcaagca ccaagactat 900
ataaaccgct ttatatacga gagtgtatat catggacatc ttaggaggag tgagacaaag 960
gggtggggcg gaggactcaa tgatgaagac tgcagacgga gggtagggag ggagggcagc 1020
gcagacaggc gaggcgaagg agagtgagaa agtagtggag ttatcagcga ggagctttca 1080
cgggtaggag gaggaagat agttgtggag gaggaacgac gcgtggagcg ggggtgaggg 1140
gaggcaagat agtgggtgtg gagaccgatt gacgaggggc agggga 1186

<210> 165
<211> 96
<212> PRT

146

<213> Homo sapien

<400> 165

Met Ala Phe Ile Leu Ala Arg Thr Val Gln Ile Val Thr Arg Lys Ile
1 5 10 15

Arg Asp Gly Lys Tyr Glu Gln Leu Tyr Phe Asn Arg Cys Arg Lys Gln
20 25 30

Ile Phe Phe Thr Val Glu Ile Trp Leu Leu Asn Leu Trp Gly Leu His
35 40 45

Thr Ser His Leu Glu Thr Arg Leu Gly Gln Leu His Val Glu Arg Asn
50 55 60

Asn Leu Leu Pro Asp His Ile Ser Thr Leu Lys Glu Val Phe Ile Thr
65 70 75 80

Arg Leu Phe Phe Leu Lys Thr Pro Asn Arg Pro Arg Val Thr Lys Asn
85 90 95

<210> 166

<211> 54

<212> PRT

<213> Homo sapien

<400> 166

Met Cys Arg Val Pro Ser Pro Lys Val Asn Leu Glu Pro Leu Asp Asn
1 5 10 15

Thr Asn Lys Asn Ile Tyr Phe Thr Ser Val Ile Tyr Leu Glu Asn Val
20 25 30

Leu Ser Ile Leu His Ile Phe Leu Ile Lys Ser Thr Gly Asp His Cys
35 40 45

Glu Val Asp Ile Leu Phe
50

<210> 167

<211> 50

<212> PRT

<213> Homo sapien

<400> 167

Met Val Phe Tyr Tyr Tyr Tyr Gly Phe Lys Lys Ser Asn Phe Ile

147

1 5 10 15
 Ser Phe Cys Lys Glu Leu Ser Asn Ile Leu Tyr Arg Phe Cys Glu Arg
 20 25 30
 Thr Tyr Phe Leu Thr Val Ile Phe Ile Ser Phe Lys Ile Phe Val Ser
 35 40 45
 His Leu
 50
 <210> 168
 <211> 229
 <212> PRT
 <213> Homo sapien
 <400> 168
 Met Ala Glu Glu Met Glu Ser Ser Leu Glu Ala Ser Phe Ser Ser Ser
 1 5 10 15
 Gly Ala Val Ser Gly Ala Ser Gly Phe Leu Pro Pro Ala Arg Ser Arg
 20 25 30
 Ile Phe Lys Ile Ile Val Ile Gly Asp Ser Asn Val Gly Lys Thr Cys
 35 40 45
 Leu Thr Tyr Arg Phe Cys Ala Gly Arg Phe Pro Asp Arg Thr Glu Ala
 50 55 60
 Thr Ile Gly Val Asp Phe Arg Glu Arg Ala Val Glu Ile Asp Gly Glu
 65 70 75 80
 Arg Ile Lys Ile Gln Leu Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg
 85 90 95
 Lys Ser Met Val Gln His Tyr Tyr Arg Asn Val His Ala Val Val Phe
 100 105 110
 Val Tyr Asp Met Thr Asn Met Ala Ser Phe His Ser Leu Pro Ser Trp
 115 120 125
 Ile Glu Glu Cys Lys Gln His Leu Leu Ala Asn Asp Ile Pro Arg Ile
 130 135 140
 Leu Val Gly Asn Lys Cys Asp Leu Arg Ser Ala Ile Gln Val Pro Thr

148

145 150 155 160

Asp Leu Ala Gln Lys Phe Ala Asp Thr His Ser Met Pro Leu Phe Glu
 165 170 175

Thr Ser Ala Lys Asn Pro Asn Asp Asn Asp His Val Glu Ala Ile Phe
 180 185 190

Met Thr Leu Ala His Lys Leu Lys Ser His Lys Pro Leu Met Leu Ser
 195 200 205

Gln Pro Pro Asp Asn Gly Ile Ile Leu Lys Pro Glu Pro Lys Pro Ala
 210 215 220

Met Thr Cys Trp Cys
 225

<210> 169
 <211> 56
 <212> PRT
 <213> Homo sapien

<400> 169

Met Tyr Leu Lys Glu Lys Tyr Pro Asp Leu Lys Pro Thr Ala Asp Val
 1 5 10 15

Ala Asn Phe His Thr Thr Ala Gly His Gly Ser Leu Leu Thr Thr His
 20 25 30

Cys His Leu Arg Leu Cys Leu Cys Phe Ile Gln Arg Glu Arg Gly Gly
 35 40 45

Leu Lys Gly Met Leu Pro Gly Gly
 50 55

<210> 170
 <211> 34
 <212> PRT
 <213> Homo sapien

<400> 170

Met Thr Ser Val Tyr Ala Thr Leu Gly Ser Leu Pro Asp Tyr Lys Val
 1 5 10 15

Pro Phe Met Gly Cys Thr Met Phe Thr Leu Val Ser Gln Glu Asn Ser
 20 25 30

149

Ser Ala

<210> 171
 <211> 77
 <212> PRT
 <213> Homo sapien

<400> 171

Met Val Tyr Asn Leu Tyr Ser Phe Gly Leu Lys Val Thr Thr Arg Arg
 1 5 10 15

Ile Arg Glu Ser Pro Gln Asn Pro Gly Ala Gly Leu Leu Ser Ile Leu
 20 25 30

Leu Ile Thr Leu Val Phe Ser Ser Val Asn Lys Ile Ile Leu Leu Phe
 35 40 45

Gln Lys Lys Lys Gln Lys Lys Gly Val Gly Tyr Pro Gly Pro Lys Ala
 50 55 60

Phe Pro Gly Trp Asn Leu Phe Pro Pro Ile Lys Pro Lys
 65 70 75

<210> 172
 <211> 43
 <212> PRT
 <213> Homo sapien

<400> 172

Met Gln Glu Phe Thr Trp Leu Phe Glu Lys Glu Asn Phe Lys Val Ser
 1 5 10 15

Gly Trp Thr Glu Ser His Glu Ala Arg Ser Leu Leu Thr Ala Arg Ser
 20 25 30

Leu Glu Lys Gln Val Ser Gly Ser Phe Thr Ser
 35 40

<210> 173
 <211> 39
 <212> PRT
 <213> Homo sapien

<400> 173

150

Met Thr Gln Leu Tyr Met Thr Leu Ser Ser Tyr Gln His Tyr His Asn
 1 5 10 15

Ser Asn Ile Asn Asn Tyr Asn Lys Ser His Tyr Tyr Ser Leu Glu Ala
 20 25 30

Leu Val Gln Asn Arg Phe Tyr
 35

<210> 174
 <211> 48
 <212> PRT
 <213> Homo sapien

<400> 174

Met Leu Lys Gly His Tyr Gln Tyr Gly Met Glu Asp Leu Ser Phe His
 1 5 10 15

Thr Phe Ser Ser Ser Phe Leu Asn Phe Leu Leu Leu Phe Leu Leu Ser
 20 25 30

Cys Met Val Ala Pro Phe Pro Phe Leu Leu Ser Val Pro Ser Lys Gln
 35 40 45

<210> 175
 <211> 108
 <212> PRT
 <213> Homo sapien

<400> 175

Phe Leu Lys Arg Gln Ser Ile Ser Leu Leu Pro Gln Leu Glu Cys Ser
 1 5 10 15

Gly Thr Ile Ile Val His His Thr Leu Glu Leu Leu Gly Lys Gly Ser
 20 25 30

Ser Leu Ala Ser Ala Ser Gln Val Ala Arg Tyr Thr Gly Met Cys Tyr
 35 40 45

His Ala Trp Leu Ile Lys Lys Ile Phe Leu Glu Met Arg Ser Cys Cys
 50 55 60

Val Ala Gln Ala Gly Leu Lys Leu Leu Gly Ser Asn Asn Pro Pro Thr
 65 70 75 80

Leu Ala Ser Gln Ser Ala Gly Ile Thr Gly Val Ser His Ser Thr Ala

151

85

90

95

Pro Tyr Leu Gln Ile Leu Asn Gln Ala Ile Ala Ile
 100 105

<210> 176
 <211> 48
 <212> PRT
 <213> Homo sapien

<400> 176

Met Val His Ile Thr Phe Ile Gln His Leu Leu Glu Pro Arg His Cys
 1 5 10 15

Asn Tyr Met Phe Phe Leu Val Thr Tyr Phe Val Arg Ser Cys Phe Leu
 20 25 30

Ala Thr Ser Asp Tyr Ser Lys His Arg Lys Phe Asn Lys Thr Ile Phe
 35 40 45

<210> 177
 <211> 302
 <212> PRT
 <213> Homo sapien

<400> 177

Trp Ser Ala Asn Asn Trp Glu Ile His Thr His Thr Lys Asn Leu Asn
 1 5 10 15

Pro Tyr Leu Thr Pro Asp Thr Lys Ala Thr Phe Lys Ala Ile Ile Gly
 20 25 30

Leu Thr Ala Arg Ala Lys Thr Met Gln Leu Pro Glu Ser Phe Cys Gln
 35 40 45

Lys Glu Asn Thr Gly Glu Asn Leu Ser Asp Leu Gly Val Gly Lys Asp
 50 55 60

Phe Leu Arg His Lys Lys His Glu Val Ala Arg Gly Lys Ile Ala Lys
 65 70 75 80

Leu Asp Phe Ile Gln Val Lys Asn Phe Ala Ser Leu Lys Asp Thr Phe
 85 90 95

Lys Lys Met Lys Lys Tyr Ala Leu Gly Trp Glu Lys Ile Phe Ala Glu
 100 105 110

152

Arg Val Ser Asp Arg Gly Cys Val Ser Arg Arg Tyr Lys Glu Leu Ala
 115 120 125

Thr Gln Glu Leu Lys Asp Asn Pro Ile Arg Lys Gly Gly Asn Asn Leu
 130 135 140

Asn Lys Val His Gln Arg Ile Ala Met Ala Asn Lys His Met Lys Arg
 145 150 155 160

Cys Pro Lys Ser Ala Val Ile Arg Glu Ile Ala Ile Ala Thr Ile Met
 165 170 175

Arg Tyr His Cys Ile Leu Pro Arg Met Ala Val Met Asn Ala Asp Ala
 180 185 190

Ser His Gly Asp Lys Asn Gly Gly Ser Ser Gly Thr Leu Ile His Ala
 195 200 205

Arg Ala Glu Cys Glu Met Asp Gln Leu Leu Trp Lys Thr Ile Gly Gln
 210 215 220

Phe Leu Ser Lys Val Asn Val Lys Met Pro Tyr Asp Ser Ser Ile Pro
 225 230 235 240

Phe Leu Ile Ile Gln Glu Lys Ala Asn Cys Ile Ser Thr Lys Lys Thr
 245 250 255

Cys Thr Gln Thr Phe Thr Ala Ala Ile Tyr Leu Leu Val Ile Ala Lys
 260 265 270

Asn Cys Lys Gln Leu Pro Tyr Pro Ser Ser Val Trp Ile Asn Lys Ile
 275 280 285

Trp Cys Ile Tyr Thr Met Glu Tyr Tyr Ser Ala Ile Lys Arg
 290 295 300

<210> 178

<211> 47

<212> PRT

<213> Homo sapien

<400> 178

Met Leu Thr Leu Thr Phe Cys Ile Tyr Arg His Phe Leu Tyr Phe Leu
 1 5 10 15

His Phe Ser Tyr Val Asn Pro Pro His Ser Pro His Ile Ile Ile His
20 25 30

Tyr Asp His Glu Gly Phe Ile Pro Gly Tyr Ser Leu Ile Glu Asn
35 40 45

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<210> 179
<211> 85
<212> PRT
<213> Homo sapien
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<400> 179

Met Gly Gly Asn Gly Ser Thr Cys Lys Pro Asp Thr Glu Arg Gln Gly
1 5 10 15

Thr Leu Ser Thr Ala Ala Pro Thr Thr Ser Pro Ala Pro Cys Leu Ser
20 25 30

Asn His His Asn Lys Lys His Leu Ile Leu Ala Phe Cys Ala Gly Val
35 40 45

Leu Leu Thr Leu Leu Leu Ile Ala Phe Ile Phe Leu Ile Ile Lys Ser
50 55 60

Tyr Arg Lys Tyr His Ser Lys Pro Gln Ala Pro Asp Pro His Ser Asp
65 70 75 80

Pro Pro Ala Lys Leu
85

<210>	180
<211>	102
<212>	PRT
<213>	Homo sapien

<400> 180

Asn Gly Ser Thr Cys Lys Pro Asp Thr Glu Arg Gln Gly Thr Leu Ser
1 5 10 15

Thr Ala Ala Pro Thr Thr Ser Pro Ala Pro Cys Leu Ser Asn His His
20 25 30

Asn Lys Lys His Leu Ile Leu Ala Phe Cys Ala Gly Val Leu Leu Thr
35 40 45

154

Leu Leu Leu Ile Ala Phe Ile Phe Leu Ile Ile Lys Ser Tyr Arg Lys
 50 55 60

Tyr His Ser Lys Pro Gln Ala Pro Asp Pro His Ser Asp Pro Pro Ala
 65 70 75 80

Lys Leu Ser Ser Ile Pro Gly Glu Ser Leu Thr Tyr Ala Ser Thr Thr
 85 90 95

Phe Lys Leu Ser Glu Asp
 100

<210> 181
 <211> 56
 <212> PRT
 <213> Homo sapien

<400> 181

Met Trp Ala Asp Ile Tyr Lys Asp Val Arg Arg Val Ala Gln Ser Val
 1 5 10 15

Phe Phe Phe Val Phe Phe Ser Thr Gln Ala Leu Ile His Phe Ser Asp
 20 25 30

Val Phe Pro Lys Asn Glu Thr Tyr Ile Phe Pro Gln Pro Val Leu Arg
 35 40 45

Ser Ser Lys Cys Leu Thr Lys Lys
 50 55

<210> 182
 <211> 742
 <212> PRT
 <213> Homo sapien

<400> 182

Gly Lys Pro Phe Cys Asn Asn Glu Thr Phe Gly Gln Tyr Pro Leu Gln
 1 5 10 15

Val Asn Gly Tyr Arg Asn Leu Asp Glu Cys Leu Glu Gly Ala Met Val
 20 25 30

Glu Gly Asp Val Glu Leu Leu Pro Ser Asp His Ser Val Lys Tyr Gly
 35 40 45

155

Gln Glu Arg Trp Phe Thr Lys Leu Pro Pro Val Leu Thr Phe Glu Leu
 50 55 60

Ser Arg Phe Glu Phe Asn Gln Ser Leu Gly Gln Pro Glu Lys Ile His
 65 70 75 80

Asn Lys Leu Glu Phe Pro Gln Ile Ile Tyr Met Asp Arg Tyr Met Tyr
 85 90 95

Arg Ser Lys Glu Leu Ile Arg Asn Lys Arg Glu Cys Ile Arg Lys Leu
 100 105 110

Lys Glu Glu Ile Lys Ile Leu Gln Gln Lys Leu Glu Arg Tyr Val Lys
 115 120 125

Tyr Gly Ser Gly Pro Ala Arg Phe Pro Leu Pro Asp Met Leu Lys Tyr
 130 135 140

Val Ile Glu Phe Ala Ser Thr Lys Pro Ala Ser Glu Ser Cys Pro Pro
 145 150 155 160

Glu Ser Asp Thr His Met Thr Leu Pro Leu Ser Ser Val His Cys Ser
 165 170 175

Val Ser Asp Gln Thr Ser Lys Glu Ser Thr Ser Thr Glu Ser Ser Ser
 180 185 190

Gln Asp Val Glu Ser Thr Phe Ser Ser Pro Glu Asp Ser Leu Pro Lys
 195 200 205

Ser Lys Pro Leu Thr Ser Ser Arg Ser Ser Met Glu Met Pro Ser Gln
 210 215 220

Pro Ala Pro Arg Thr Val Thr Asp Glu Glu Ile Asn Phe Val Lys Thr
 225 230 235 240

Cys Leu Gln Arg Trp Arg Ser Glu Ile Glu Gln Asp Ile Gln Asp Leu
 245 250 255

Lys Thr Cys Ile Ala Ser Thr Thr Gln Thr Ile Glu Gln Met Tyr Cys
 260 265 270

Asp Pro Leu Leu Arg Gln Val Pro Tyr Arg Leu His Ala Val Leu Val
 275 280 285

156

His Glu Gly Gln Ala Asn Ala Gly His Tyr Trp Ala Tyr Ile Tyr Asn
 290 295 300

Gln Pro Arg Gln Ser Trp Leu Lys Tyr Asn Asp Ile Ser Val Thr Glu
 305 310 315 320

Ser Ser Trp Glu Glu Val Glu Arg Asp Ser Tyr Gly Gly Leu Arg Asn
 325 330 335

Val Ser Ala Tyr Cys Leu Met Tyr Ile Asn Asp Lys Leu Pro Tyr Phe
 340 345 350

Asn Ala Glu Ala Ala Pro Thr Glu Ser Asp Gln Met Ser Glu Val Glu
 355 360 365

Ala Leu Ser Val Glu Leu Lys His Tyr Ile Gln Glu Asp Asn Trp Arg
 370 375 380

Phe Glu Gln Glu Val Glu Glu Trp Glu Glu Glu Gln Ser Cys Lys Ile
 385 390 395 400

Pro Gln Met Glu Ser Ser Thr Asn Ser Ser Ser Gln Asp Tyr Ser Thr
 405 410 415

Ser Gln Glu Pro Ser Val Ala Ser Ser His Gly Val Arg Cys Leu Ser
 420 425 430

Ser Glu His Ala Val Ile Val Lys Glu Gln Thr Ala Gln Ala Ile Ala
 435 440 445

Asn Thr Ala Arg Ala Tyr Glu Lys Ser Gly Val Glu Ala Ala Leu Ser
 450 455 460

Glu Ala Phe His Glu Glu Tyr Ser Arg Leu Tyr Gln Leu Ala Lys Glu
 465 470 475 480

Thr Pro Thr Ser His Ser Asp Pro Arg Leu Gln His Val Leu Val Tyr
 485 490 495

Phe Phe Gln Asn Glu Ala Pro Lys Arg Val Val Glu Arg Thr Leu Leu
 500 505 510

Glu Gln Phe Ala Asp Lys Asn Leu Ser Tyr Asp Glu Arg Ser Ile Ser
 515 520 525

157

Ile Met Lys Val Ala Gln Ala Lys Leu Lys Glu Ile Gly Pro Asp Asp
 530 535 540

Met Asn Met Glu Glu Tyr Lys Lys Trp His Glu Asp Tyr Ser Leu Phe
 545 550 555 560

Arg Lys Val Ser Val Tyr Leu Leu Thr Gly Leu Glu Leu Tyr Gln Lys
 565 570 575

Gly Lys Tyr Gln Glu Ala Leu Ser Tyr Leu Val Tyr Ala Tyr Gln Ser
 580 585 590

Asn Ala Ala Leu Leu Met Lys Gly Pro Arg Arg Gly Val Lys Glu Ser
 595 600 605

Val Ile Ala Leu Tyr Arg Arg Lys Cys Leu Leu Glu Leu Asn Ala Lys
 610 615 620

Ala Ala Ser Leu Phe Glu Thr Asn Asp Asp His Ser Val Thr Glu Gly
 625 630 635 640

Ile Asn Val Met Asn Glu Leu Ile Ile Pro Cys Ile His Leu Ile Ile
 645 650 655

Asn Asn Asp Ile Ser Lys Asp Asp Leu Asp Ala Ile Glu Val Met Arg
 660 665 670

Asn His Trp Cys Ser Tyr Leu Gly Gln Asp Ile Ala Glu Asn Leu Gln
 675 680 685

Leu Cys Leu Gly Glu Phe Leu Pro Arg Leu Leu Asp Pro Ser Ala Glu
 690 695 700

Ile Ile Val Leu Lys Glu Pro Pro Thr Ile Arg Pro Asn Ser Pro Tyr
 705 710 715 720

Asp Leu Cys Ser Arg Phe Ala Ala Val Met Glu Ser Ile Gln Gly Val
 725 730 735

Ser Thr Val Thr Val Lys
 740

<210> 183

158

<211> 50
 <212> PRT
 <213> Homo sapien

<400> 183

Met Met Tyr Val Cys Ile Phe His Tyr Ile Phe Leu Phe Phe Tyr Asn
 1 5 10 15

Trp Val Leu Asn Ile Phe Gly Arg Lys Ile Ile Ile Leu Ser Leu Leu
 20 25 30

Lys Ile Asn Met His Asn Leu Pro Leu Tyr Ile Ala Tyr Asn Ile Leu
 35 40 45

Met Met
 50

<210> 184
 <211> 1518
 <212> PRT
 <213> Homo sapien

<400> 184

Met Cys Lys Lys Leu Ser Gly Asn His Leu Asn Pro Glu Pro Asn Gln
 1 5 10 15

Pro Ala Pro Ser Val Asp Leu Asp Phe Leu Glu Asp Asp Ile Leu Gly
 20 25 30

Ser Pro Ala Thr Gly Gly Gly Gly Gly Gly Ser Gly Gly Ala Asp Gln
 35 40 45

Pro Cys Asp Ile Leu Gln Gln Ser Leu Gln Glu Ala Asn Ile Thr Glu
 50 55 60

Gln Thr Leu Glu Ala Glu Ala Glu Leu Asp Leu Gly Pro Phe Gln Leu
 65 70 75 80

Pro Thr Leu Gln Pro Ala Asp Gly Gly Ala Gly Pro Thr Gly Ala Gly
 85 90 95

Gly Ala Ala Ala Val Ala Ala Gly Pro Gln Ala Leu Phe Pro Gly Ser
 100 105 110

Thr Asp Leu Leu Gly Leu Gln Gly Pro Pro Thr Val Leu Thr His Gln
 115 120 125

159

Ala Leu Val Pro Pro Gln Asp Val Val Asn Lys Ala Leu Ser Val Gln
 130 135 140

Pro Phe Leu Gln Pro Val Gly Leu Gly Asn Val Thr Leu Gln Pro Ile
 145 150 155 160

Pro Gly Leu Gln Gly Leu Pro Asn Gly Ser Pro Gly Gly Ala Thr Ala
 165 170 175

Ala Thr Leu Gly Leu Ala Pro Ile Gln Val Val Gly Gln Pro Val Met
 180 185 190

Ala Leu Asn Thr Pro Thr Ser Gln Leu Leu Ala Lys Gln Val Pro Val
 195 200 205

Ser Gly Tyr Leu Ala Ser Ala Ala Gly Pro Ser Glu Pro Val Thr Leu
 210 215 220

Ala Ser Ala Gly Val Ser Pro Gln Gly Ala Gly Leu Val Ile Gln Lys
 225 230 235 240

Asn Leu Ser Ala Ala Val Ala Thr Thr Leu Asn Gly Asn Ser Val Phe
 245 250 255

Gly Gly Ala Gly Ala Ala Ser Ala Pro Thr Gly Thr Pro Ser Gly Gln
 260 265 270

Pro Leu Ala Val Ala Pro Gly Leu Gly Ser Ser Pro Leu Val Pro Ala
 275 280 285

Pro Asn Val Ile Leu His Arg Thr Pro Thr Pro Ile Gln Pro Lys Pro
 290 295 300

Ala Gly Val Leu Pro Pro Lys Leu Tyr Gln Leu Thr Pro Lys Pro Phe
 305 310 315 320

Ala Pro Ala Gly Ala Thr Leu Thr Ile Gln Gly Glu Pro Gly Ala Leu
 325 330 335

Pro Gln Gln Pro Lys Ala Pro Gln Asn Leu Thr Phe Met Ala Ala Gly
 340 345 350

Lys Ala Gly Gln Asn Val Val Leu Ser Gly Phe Pro Ala Pro Ala Leu

160

355

360

365

Gln Ala Asn Val Phe Lys Gln Pro Pro Ala Thr Thr Thr Gly Ala Ala
 370 375 380

Pro Pro Gln Pro Pro Gly Ala Leu Ser Lys Pro Met Ser Val His Leu
 385 390 395 400

Leu Asn Gln Gly Ser Ser Ile Val Ile Pro Ala Gln His Met Leu Pro
 405 410 415

Gly Gln Asn Gln Phe Leu Leu Pro Gly Ala Pro Ala Val Gln Leu Pro
 420 425 430

Gln Gln Leu Ser Ala Leu Pro Ala Asn Val Gly Gly Gln Ile Leu Ala
 435 440 445

Ala Ala Ala Pro His Thr Gly Gly Gln Leu Ile Ala Asn Pro Ile Leu
 450 455 460

Thr Asn Gln Asn Leu Ala Gly Pro Leu Ser Leu Gly Pro Val Leu Ala
 465 470 475 480

Pro His Ser Gly Ala His Ser Ala His Ile Leu Ser Ala Ala Pro Ile
 485 490 495

Gln Val Gly Gln Pro Ala Leu Phe Gln Met Pro Val Ser Leu Ala Ala
 500 505 510

Gly Ser Leu Pro Thr Gln Ser Gln Pro Ala Pro Ala Gly Pro Ala Ala
 515 520 525

Thr Thr Val Leu Gln Gly Val Thr Leu Pro Pro Ser Ala Val Ala Met
 530 535 540

Leu Asn Thr Pro Asp Gly Leu Val Gln Pro Ala Thr Pro Ala Ala Ala
 545 550 555 560

Thr Gly Glu Ala Ala Pro Val Leu Thr Val Gln Pro Ala Pro Gln Ala
 565 570 575

Pro Pro Ala Val Ser Thr Pro Leu Pro Leu Gly Leu Gln Gln Pro Gln
 580 585 590

161

Ala Gln Gln Pro Pro Gln Ala Pro Thr Pro Gln Ala Ala Ala Pro Pro
 595 600 605

Gln Ala Thr Thr Pro Gln Pro Ser Pro Gly Leu Ala Ser Ser Pro Glu
 610 615 620

Lys Ile Val Leu Gly Gln Pro Pro Ser Ala Thr Pro Thr Ala Ile Leu
 625 630 635 640

Thr Gln Asp Ser Leu Gln Met Phe Leu Pro Gln Glu Arg Ser Gln Gln
 645 650 655

Pro Leu Ser Ala Glu Gly Pro His Leu Ser Val Pro Ala Ser Val Ile
 660 665 670

Val Ser Ala Pro Pro Pro Ala Gln Asp Pro Ala Pro Ala Thr Pro Val
 675 680 685

Ala Lys Gly Ala Gly Leu Gly Pro Gln Ala Pro Asp Ser Gln Ala Ser
 690 695 700

Pro Ala Pro Ala Pro Gln Ile Pro Ala Ala Ala Pro Leu Lys Gly Pro
 705 710 715 720

Gly Pro Ser Ser Ser Pro Ser Leu Pro His Gln Ala Pro Leu Gly Asp
 725 730 735

Ser Pro His Leu Pro Ser Pro His Pro Thr Arg Pro Pro Ser Arg Pro
 740 745 750

Pro Ser Arg Pro Gln Ser Val Ser Arg Pro Pro Ser Glu Pro Pro Leu
 755 760 765

His Pro Cys Pro Pro Pro Gln Ala Pro Pro Thr Leu Pro Gly Ile Phe
 770 775 780

Val Ile Gln Asn Gln Leu Gly Val Pro Pro Pro Ala Ser Asn Pro Ala
 785 790 795 800

Pro Thr Ala Pro Gly Pro Pro Gln Pro Pro Leu Arg Pro Gln Ser Gln
 805 810 815

Pro Pro Glu Gly Pro Leu Pro Pro Ala Pro His Leu Pro Pro Ser Ser
 820 825 830

162

Thr Ser Ser Ala Val Ala Ser Ser Ser Glu Thr Ser Ser Arg Leu Pro
 835 840 845

Ala Pro Thr Pro Ser Asp Phe Gln Leu Gln Phe Pro Pro Ser Gln Gly
 850 855 860

Pro His Lys Ser Pro Thr Pro Pro Pro Thr Leu His Leu Val Pro Glu
 865 870 875 880

Pro Ala Ala Pro Pro Pro Pro Pro Arg Thr Phe Gln Met Val Thr
 885 890 895

Thr Pro Phe Pro Ala Leu Pro Gln Pro Lys Ala Leu Leu Glu Arg Phe
 900 905 910

His Gln Val Pro Ser Gly Ile Ile Leu Gln Asn Lys Ala Gly Gly Ala
 915 920 925

Pro Ala Ala Pro Gln Thr Ser Thr Ser Leu Gly Pro Leu Thr Ser Pro
 930 935 940

Ala Ala Ser Val Leu Val Ser Gly Gln Ala Pro Ser Gly Thr Pro Thr
 945 950 955 960

Ala Pro Ser His Ala Pro Ala Pro Ala Pro Met Ala Ala Thr Gly Leu
 965 970 975

Pro Pro Leu Leu Pro Ala Glu Asn Lys Ala Phe Ala Ser Asn Leu Pro
 980 985 990

Thr Leu Asn Val Ala Lys Ala Ala Ser Ser Gly Pro Gly Lys Pro Ser
 995 1000 1005

Gly Leu Gln Tyr Glu Ser Lys Leu Ser Gly Leu Lys Lys Pro Pro
 1010 1015 1020

Thr Leu Gln Pro Ser Lys Glu Ala Cys Phe Leu Glu His Leu His
 1025 1030 1035

Lys His Gln Gly Ser Val Leu His Pro Asp Tyr Lys Thr Ala Phe
 1040 1045 1050

Pro Ser Phe Glu Asp Ala Leu His Arg Leu Leu Pro Tyr His Val
 1055 1060 1065

163

Tyr	Gln	Gly	Ala	Leu	Pro	Ser	Pro	Ser	Asp	Tyr	His	Lys	Val	Asp
1070						1075					1080			
Glu	Glu	Phe	Glu	Thr	Val	Ser	Thr	Gln	Leu	Leu	Lys	Arg	Thr	Gln
1085						1090					1095			
Ala	Met	Leu	Asn	Lys	Tyr	Arg	Leu	Leu	Leu	Leu	Glu	Glu	Ser	Arg
1100						1105					1110			
Arg	Val	Ser	Pro	Ser	Ala	Glu	Met	Val	Met	Ile	Asp	Arg	Met	Phe
1115						1120					1125			
Ile	Gln	Glu	Glu	Lys	Thr	Thr	Leu	Ala	Leu	Asp	Lys	Gln	Leu	Ala
1130						1135					1140			
Lys	Glu	Lys	Pro	Asp	Glu	Tyr	Val	Ser	Ser	Ser	Arg	Ser	Leu	Gly
1145						1150					1155			
Leu	Pro	Ile	Ala	Ala	Ser	Ser	Glu	Gly	His	Arg	Leu	Pro	Gly	His
1160						1165					1170			
Gly	Pro	Leu	Ser	Ser	Ser	Ala	Pro	Gly	Ala	Ser	Thr	Gln	Pro	Pro
1175						1180					1185			
Pro	His	Leu	Pro	Thr	Lys	Leu	Val	Ile	Arg	His	Gly	Gly	Ala	Gly
1190						1195					1200			
Gly	Ser	Pro	Ser	Val	Thr	Trp	Ala	Arg	Ala	Ser	Ser	Ser	Leu	Ser
1205						1210					1215			
Ser	Ser	Ser	Ser	Ser	Ser	Ser	Ala	Ala	Ser	Ser	Leu	Asp	Ala	Asp
1220						1225					1230			
Glu	Asp	Gly	Pro	Met	Pro	Ser	Arg	Asn	Arg	Pro	Pro	Ile	Lys	Thr
1235						1240					1245			
Tyr	Glu	Ala	Arg	Ser	Arg	Ile	Gly	Leu	Lys	Leu	Lys	Ile	Lys	Gln
1250						1255					1260			
Glu	Ala	Gly	Leu	Ser	Lys	Val	Val	His	Asn	Thr	Ala	Leu	Asp	Pro
1265						1270					1275			
Val	His	Gln	Pro	Pro	Pro	Pro	Pro	Ala	Thr	Leu	Lys	Val	Ala	Glu

164

1280		1285		1290
Pro Pro Pro Arg Pro Pro Pro Pro Pro Pro Pro Thr Gly Gln Met				
1295		1300		1305
Asn Gly Thr Val Asp His Pro Pro Pro Ala Ala Pro Glu Arg Lys				
1310		1315		1320
Pro Leu Gly Thr Ala Pro His Cys Pro Arg Leu Pro Leu Arg Lys				
1325		1330		1335
Thr Tyr Arg Glu Asn Val Gly Gly Pro Gly Ala Pro Glu Gly Thr				
1340		1345		1350
Pro Ala Gly Arg Ala Arg Gly Gly Ser Pro Ala Pro Leu Pro Ala				
1355		1360		1365
Lys Val Asp Glu Ala Thr Ser Gly Leu Ile Arg Glu Leu Ala Ala				
1370		1375		1380
Val Glu Asp Glu Leu Tyr Gln Arg Met Leu Lys Gly Pro Pro Pro				
1385		1390		1395
Glu Pro Ala Ala Ser Ala Ala Gln Gly Thr Gly Asp Pro Asp Trp				
1400		1405		1410
Glu Ala Pro Gly Leu Pro Pro Ala Lys Arg Arg Lys Ser Glu Ser				
1415		1420		1425
Pro Asp Val Asp Gln Ala Ser Phe Ser Ser Asp Ser Pro Gln Asp				
1430		1435		1440
Asp Thr Leu Thr Glu His Leu Gln Ser Ala Ile Asp Ser Ile Leu				
1445		1450		1455
Asn Leu Gln Gln Ala Pro Gly Arg Thr Pro Ala Pro Ser Tyr Pro				
1460		1465		1470
His Ala Ala Ser Ala Gly Thr Pro Ala Ser Pro Pro Pro Leu His				
1475		1480		1485
Arg Pro Glu Ala Tyr Pro Pro Ser Ser His Asn Gly Gly Leu Gly				
1490		1495		1500

165

Ala Arg Thr Leu Thr Arg Gly Leu Gly Ala Arg Thr Leu Thr Arg
1505 1510 1515

<210> 185
<211> 42
<212> PRT
<213> Homo sapien

<400> 185

Met Lys His Gly Ser Phe Tyr Phe Thr Val Ser Asn Leu Ile Ala Ser
1 5 10 15

His Leu Lys Ser Ala Lys Ile Glu Leu Pro Lys Lys Cys Tyr Met Pro
20 25 30

Lys Gly Ala His Asn Tyr Leu Met Ala Asn
35 40

<210> 186
<211> 96
<212> PRT
<213> Homo sapien

<400> 186

Met Met Leu Gly Gln Asp Ser Ile Leu Asn Gln Ser Asn Ser Ile Phe
1 5 10 15

Gly Cys Ile Phe Tyr Thr Leu Gln Leu Leu Gly Cys Leu Arg Thr
20 25 30

Arg Trp Ala Ser Val Leu Ile Leu Leu Ser Ser Leu Val Ser Leu Ala
35 40 45

Gly Ser Val Tyr Leu Ala Trp Ile Leu Phe Phe Val Leu Tyr Asp Phe
50 55 60

Cys Ile Val Cys Ile Thr Thr Tyr Ala Ile Asn Val Ser Leu Met Trp
65 70 75 80

Leu Ser Phe Arg Lys Val Gln Glu Pro Gln Gly Lys Ala Lys Arg His
85 90 95

<210> 187
<211> 105
<212> PRT
<213> Homo sapien

166

<400> 187

Trp Gly Arg Gly Ile Gly Leu Val Glu His Val Leu Gly Gln Asp Ser
1 5 10 15

Ile Leu Asn Gln Ser Asn Ser Ile Phe Gly Cys Ile Phe Tyr Thr Leu
20 25 30

Gln Leu Leu Leu Gly Cys Leu Arg Thr Arg Trp Ala Ser Val Leu Met
35 40 45

Leu Leu Ser Ser Leu Val Ser Leu Ala Gly Ser Val Tyr Leu Ala Trp
50 55 60

Ile Leu Phe Phe Val Leu Tyr Asp Phe Cys Ile Val Cys Ile Thr Thr
65 70 75 80

Tyr Ala Ile Asn Val Ser Leu Met Trp Leu Ser Phe Arg Lys Val Gln
85 90 95

Glu Pro Gln Gly Lys Ala Lys Arg His
100 105

<210> 188

<211> 59

<212> PRT

<213> Homo sapien

<400> 188

Met Gly Lys Lys Ala His Arg His Leu Gln Phe Thr Ser Phe Lys Phe
1 5 10 15

Leu Lys Lys Thr Pro Gln Lys Lys Pro Phe Leu Pro Gly Lys Ala His
20 25 30

Glu Ile Asn Tyr Arg Ile Glu Leu Tyr Asn Ser Thr Ser Thr Ser Leu
35 40 45

Thr Leu Met Cys Phe Ala Lys Asn Leu Glu Lys
50 55

<210> 189

<211> 400

<212> PRT

<213> Homo sapien

<400> 189

167

Met Ala Trp Arg Arg Arg Glu Ala Gly Val Gly Ala Arg Gly Val Leu
 1 5 10 15

Ala Leu Ala Leu Leu Ala Leu Ala Leu Cys Val Pro Gly Ala Arg Gly
 20 25 30

Arg Ala Leu Glu Trp Phe Ser Ala Val Val Asn Ile Glu Tyr Val Asp
 35 40 45

Pro Gln Thr Asn Leu Thr Val Trp Ser Val Ser Glu Ser Gly Arg Phe
 50 55 60

Gly Asp Ser Ser Pro Lys Glu Gly Ala His Gly Leu Val Gly Val Pro
 65 70 75 80

Trp Ala Pro Gly Gly Asp Leu Glu Gly Cys Ala Pro Asp Thr Arg Phe
 85 90 95

Phe Val Pro Glu Pro Gly Gly Arg Gly Ala Ala Pro Trp Val Ala Leu
 100 105 110

Val Ala Arg Gly Gly Cys Thr Phe Lys Asp Lys Val Leu Val Ala Ala
 115 120 125

Arg Arg Asn Ala Ser Ala Val Val Leu Tyr Asn Glu Glu Arg Tyr Gly
 130 135 140

Asn Ile Thr Leu Pro Met Ser His Ala Gly Thr Gly Asn Ile Val Val
 145 150 155 160

Ile Met Ile Ser Tyr Pro Lys Gly Arg Glu Ile Leu Glu Leu Val Gln
 165 170 175

Lys Gly Ile Pro Val Thr Met Thr Ile Gly Val Gly Thr Arg His Val
 180 185 190

Gln Glu Phe Ile Ser Gly Gln Ser Val Val Phe Val Ala Ile Ala Phe
 195 200 205

Ile Thr Met Met Ile Ile Ser Leu Ala Trp Leu Ile Phe Tyr Tyr Ile
 210 215 220

Gln Arg Phe Leu Tyr Thr Gly Ser Gln Ile Gly Ser Gln Ser His Arg
 225 230 235 240

168

Lys Glu Thr Lys Lys Val Ile Gly Gln Leu Leu Leu His Thr Val Lys
245 250 255

His Gly Glu Lys Gly Ile Asp Val Asp Ala Glu Asn Cys Ala Val Cys
260 265 270

Ile Glu Asn Phe Lys Val Lys Asp Ile Ile Arg Ile Leu Pro Cys Lys
275 280 285

His Ile Phe His Arg Ile Cys Ile Asp Pro Trp Leu Leu Asp His Arg
290 295 300

Thr Cys Pro Met Cys Lys Leu Asp Val Ile Lys Ala Leu Gly Tyr Trp
305 310 315 320

Gly Glu Pro Gly Asp Val Gln Glu Met Pro Ala Pro Glu Ser Pro Pro
325 330 335

Gly Arg Asp Pro Ala Ala Asn Leu Ser Leu Ala Leu Pro Asp Asp Asp
340 345 350

Gly Ser Asp Glu Ser Ser Pro Pro Ser Ala Ser Pro Ala Glu Ser Glu
355 360 365

Pro Gln Cys Asp Pro Ser Phe Lys Gly Asp Ala Gly Glu Asn Thr Ala
370 375 380

Leu Leu Glu Ala Gly Arg Ser Asp Ser Arg His Gly Gly Pro Ile Ser
385 390 395 400

<210> 190

<211> 46

<212> PRT

<213> Homo sapien

<400> 190

Met Gly Glu Leu Gly Pro Gly Lys Lys Phe Pro Pro Gly Thr Pro Leu
1 5 10 15

Trp Pro Arg Val Pro Gln Ala Phe Phe Phe Phe Phe Leu Phe Phe Phe
20 25 30

Phe Phe Gln Cys Ile Ser Ser Met Phe Leu Leu Gly Lys Asn
35 40 45

169

<210> 191
<211> 37
<212> PRT
<213> Homo sapien

<400> 191

Met Asn Ile Pro Thr Asn Ala Tyr Asp Leu Gly Tyr Gln Cys Ile Leu
1 5 10 15

Ser His Leu Gly Phe Cys Phe Cys Leu Ser Val Tyr Trp Lys Leu Val
20 25 30

Pro Arg Arg Asp His
35

<210> 192
<211> 60
<212> PRT
<213> Homo sapien

<400> 192

Met Val Pro Phe Lys Glu Lys Asn Thr Lys Gln Gln Lys Thr Thr Ala
1 5 10 15

Gln Asp Gly Lys His Arg Asp Lys Pro Arg Thr Thr Gly Glu Asn Lys
20 25 30

Lys Asn Arg Thr Glu Ile Gln Gln Lys Asn Pro Lys Gln Arg Glu Thr
35 40 45

Gln Pro Gln Gln Arg Gly Glu Lys Lys Lys Ala Lys
50 55 60

<210> 193
<211> 81
<212> PRT
<213> Homo sapien

<400> 193

Met Lys Ile Cys Lys Arg Leu Phe Tyr Val Val Ala Leu Ile Pro Tyr
1 5 10 15

Thr Gln Gln Leu Pro Val Leu Gly Thr Phe Gln Ile Ser Asp Leu Arg
20 25 30

170

Glu Gln Thr Val Phe Ser Ala Ser Tyr Gly Ala Met Gln Ala Leu Pro
 35 40 45

Arg Pro Trp Leu Ser Pro Lys Ser His Val Leu Ser Val Leu His Leu
 50 55 60

Lys Arg Val Arg Glu Arg Arg Gly Gly Glu Lys Gly Ala Ser Gly Ala
 65 70 75 80

Arg

<210> 194
 <211> 80
 <212> PRT
 <213> Homo sapien

<400> 194

Met Gly Met Gln Val Pro Cys Ile Ser Trp Tyr Leu Ser Ala Phe Pro
 1 5 10 15

Leu Ala Ala Pro Pro Thr Arg Gly Arg Phe Leu Leu Asp Cys Lys Cys
 20 25 30

Leu Phe Ser Leu Asp Ser Ala Leu Thr Ala Pro Pro Pro Gly Arg Pro
 35 40 45

Ser Arg Thr Ser Ser Ser Gly Ser Ser Ser Ser Asp Pro Ile Gly Thr
 50 55 60

Pro Asp Leu Asn Leu Phe Pro Gly Ser Arg Ala Cys Ser Pro Ser Gln
 65 70 75 80

<210> 195
 <211> 101
 <212> PRT
 <213> Homo sapien

<400> 195

Phe Leu Phe Phe Phe Phe Leu Leu Arg Gln Asn Leu Ala Leu Val Thr
 1 5 10 15

Gln Ala Gly Val Gln Trp Tyr Asp Leu Ser Ser Leu Gln Pro Gln Arg
 20 25 30

Pro Gly Phe Lys Arg Phe Ser Cys Leu Ser Trp Asp His Arg Arg Pro

171

35

40

45

Pro Pro Cys Leu Ala Asn Phe Gly Ile Val Val Glu Met Gly Phe His
 50 55 60

His Val Gly Gln Ala Gly Leu Glu Leu Leu Thr Ser Ser Asp Pro Pro
 65 70 75 80

Thr Ser Ala Ser Gln Thr Ala Gly Ile Thr Gly Met Ser His Leu Ala
 85 90 95

Arg Leu Thr Arg Ser
 100

<210> 196
 <211> 16
 <212> PRT
 <213> Homo sapien

<400> 196

Met Pro His Val Val Leu Lys Thr Leu Pro Ser Leu Pro Ala Pro Pro
 1 5 10 15

<210> 197
 <211> 78
 <212> PRT
 <213> Homo sapien

<400> 197

Met Glu Val Ile Ser Ser Phe Leu Gly Ser Lys Leu Lys Gly Gly Gly
 1 5 10 15

Ser Phe Val Asn Thr Thr Asn Tyr Ile Arg Lys Ala Ser Pro Ile Pro
 20 25 30

His Ser Lys Ser Ile Thr Ala Leu Glu Met Ser Asn Asn Asp Leu Ser
 35 40 45

Cys Ser Arg Leu Lys Gln Arg Pro Cys His Met Ile Val Leu Gly Leu
 50 55 60

Asn Val Cys Gly Pro Val Leu Tyr Thr Leu Val Pro Asp Pro
 65 70 75

<210> 198
 <211> 928

172

<212> PRT

<213> Homo sapien

<400> 198

Asn Leu Cys Ser Leu Ile Ile Pro Leu Arg Glu Val Thr Ile Val Glu
 1 5 10 15

Lys Ala Asp Ser Ser Ser Val Leu Pro Ser Pro Leu Ser Ile Ser Thr
 20 25 30

Arg Asn Arg Met Thr Phe Leu Phe Ala Asn Leu Lys Asp Arg Asp Phe
 35 40 45

Leu Val Gln Arg Ile Ser Asp Phe Leu Gln Gln Thr Thr Ser Lys Ile
 50 55 60

Tyr Ser Asp Lys Glu Phe Ala Gly Ser Tyr Asn Ser Ser Asp Asp Glu
 65 70 75 80

Val Tyr Ser Arg Pro Ser Ser Leu Val Ser Ser Ser Pro Gln Arg Ser
 85 90 95

Thr Ser Ser Asp Ala Asp Gly Glu Arg Gln Phe Asn Leu Asn Gly Asn
 100 105 110

Ser Val Pro Thr Ala Thr Gln Thr Leu Met Thr Met Tyr Arg Arg Arg
 115 120 125

Ser Pro Glu Glu Phe Asn Pro Lys Leu Ala Lys Glu Phe Leu Lys Glu
 130 135 140

Gln Ala Trp Lys Ile His Phe Ala Glu Tyr Gly Gln Gly Ile Cys Met
 145 150 155 160

Tyr Arg Thr Glu Lys Thr Arg Glu Leu Val Leu Lys Gly Ile Pro Glu
 165 170 175

Ser Met Arg Gly Glu Leu Trp Leu Leu Leu Ser Gly Ala Ile Asn Glu
 180 185 190

Lys Ala Thr His Pro Gly Tyr Tyr Glu Asp Leu Val Glu Lys Ser Met
 195 200 205

Gly Lys Tyr Asn Leu Ala Thr Glu Glu Ile Glu Arg Asp Leu His Arg
 210 215 220

173

Ser Leu Pro Glu His Pro Ala Phe Gln Asn Glu Met Gly Ile Ala Ala
 225 230 235 240

Leu Arg Arg Val Leu Thr Ala Tyr Ala Phe Arg Asn Pro Asn Ile Gly
 245 250 255

Tyr Cys Gln Ala Met Asn Ile Val Thr Ser Val Leu Leu Leu Tyr Ala
 260 265 270

Lys Glu Glu Glu Ala Phe Trp Leu Leu Val Ala Leu Cys Glu Arg Met
 275 280 285

Leu Pro Asp Tyr Tyr Asn Thr Arg Val Val Gly Ala Leu Val Asp Gln
 290 295 300

Gly Val Phe Glu Glu Leu Ala Arg Asp Tyr Val Pro Gln Leu Tyr Asp
 305 310 315 320

Cys Met Gln Asp Leu Gly Val Ile Ser Thr Ile Ser Leu Ser Trp Phe
 325 330 335

Leu Thr Leu Phe Leu Ser Val Met Pro Phe Glu Ser Ala Val Val Val
 340 345 350

Val Asp Cys Phe Phe Tyr Glu Gly Ile Lys Val Ile Phe Gln Leu Ala
 355 360 365

Leu Ala Val Leu Asp Ala Asn Val Asp Lys Leu Leu Asn Cys Lys Asp
 370 375 380

Asp Gly Glu Ala Met Thr Val Leu Gly Arg Tyr Leu Asp Ser Val Thr
 385 390 395 400

Asn Lys Asp Ser Thr Leu Pro Pro Ile Pro His Leu His Ser Leu Leu
 405 410 415

Ser Asp Asp Val Glu Pro Tyr Pro Glu Val Asp Ile Phe Arg Leu Ile
 420 425 430

Arg Thr Ser Tyr Glu Lys Phe Gly Thr Ile Arg Ala Asp Leu Ile Glu
 435 440 445

Gln Met Arg Phe Lys Gln Arg Leu Lys Val Ile Gln Thr Leu Glu Asp

174

450

455

460

Thr Thr Lys Arg Asn Val Val Arg Thr Ile Val Thr Glu Thr Ser Phe
 465 470 475 480

Thr Ile Asp Glu Leu Glu Glu Leu Tyr Ala Leu Phe Lys Val Ser Cys
 485 490 495

Lys Ala Glu His Leu Thr Ser Cys Tyr Trp Gly Gly Ser Ser Asn Ala
 500 505 510

Leu Asp Arg His Asp Pro Ser Leu Pro Tyr Leu Glu Gln Tyr Arg Ile
 515 520 525

Asp Phe Glu Gln Phe Lys Gly Met Phe Ala Leu Leu Phe Pro Trp Ala
 530 535 540

Cys Gly Thr His Ser Asp Val Leu Ala Ser Arg Leu Phe Gln Leu Leu
 545 550 555 560

Asp Glu Asn Gly Asp Ser Leu Ile Asn Phe Arg Glu Phe Val Ser Gly
 565 570 575

Leu Ser Ala Ala Cys His Gly Asp Leu Thr Glu Lys Leu Lys Leu Leu
 580 585 590

Tyr Lys Met His Val Leu Pro Glu Pro Ser Ser Asp Gln Asp Glu Pro
 595 600 605

Asp Ser Ala Phe Glu Ala Thr Gln Tyr Phe Phe Glu Asp Ile Thr Pro
 610 615 620

Glu Cys Thr His Val Val Gly Leu Asp Ser Arg Ser Lys Gln Gly Ala
 625 630 635 640

Asp Asp Gly Phe Val Thr Val Ser Leu Lys Pro Asp Lys Gly Lys Arg
 645 650 655

Ala Asn Ser Gln Glu Asn Arg Asn Tyr Leu Arg Leu Trp Thr Pro Glu
 660 665 670

Asn Lys Ser Lys Ser Lys Asn Ala Lys Asp Leu Pro Lys Leu Asn Gln
 675 680 685

175

Gly Gln Phe Ile Glu Leu Cys Lys Thr Met Tyr Asn Met Phe Ser Glu
 690 695 700

Asp Pro Asn Glu Gln Glu Leu Tyr His Ala Thr Ala Ala Val Thr Ser
 705 710 715 720

Leu Leu Leu Glu Ile Gly Glu Val Gly Lys Leu Phe Val Ala Gln Pro
 725 730 735

Ala Lys Glu Gly Gly Ser Gly Gly Ser Gly Pro Ser Cys His Gln Gly
 740 745 750

Ile Pro Gly Val Leu Phe Pro Lys Lys Gly Pro Gly Gln Pro Tyr Val
 755 760 765

Val Glu Ser Val Glu Pro Leu Pro Ala Ser Leu Ala Pro Asp Ser Glu
 770 775 780

Glu His Ser Leu Gly Gly Gln Met Glu Asp Ile Lys Leu Glu Asp Ser
 785 790 795 800

Ser Pro Arg Asp Asn Gly Ala Cys Ser Ser Met Leu Ile Ser Asp Asp
 805 810 815

Asp Thr Lys Asp Asp Ser Ser Met Ser Ser Tyr Ser Val Leu Ser Ala
 820 825 830

Gly Ser His Glu Glu Asp Lys Leu His Cys Glu Asp Ile Gly Glu Asp
 835 840 845

Thr Val Leu Val Arg Ser Gly Gln Gly Thr Ala Ala Leu Pro Arg Ser
 850 855 860

Thr Ser Leu Asp Arg Asp Trp Ala Ile Thr Phe Glu Gln Phe Leu Ala
 865 870 875 880

Ser Leu Leu Thr Glu Pro Ala Leu Val Lys Tyr Phe Asp Lys Pro Val
 885 890 895

Cys Met Met Ala Arg Ile Thr Ser Ala Lys Asn Ile Arg Met Met Gly
 900 905 910

Lys Pro Leu Thr Ser Ala Ser Asp Tyr Glu Ile Ser Ala Met Ser Gly
 915 920 925

176

<210> 199
 <211> 27
 <212> PRT
 <213> Homo sapien

<400> 199

Met His Val Glu Arg Arg Ser Val Met Asp Ala Trp Ser Arg Arg Gly
 1 5 10 15

Ala Gly Lys Tyr Thr Asp Ile Lys Asp Gln Ile
 20 25

<210> 200
 <211> 318
 <212> PRT
 <213> Homo sapien

<400> 200

Met Asn Arg Phe Gly Thr Arg Leu Val Gly Ala Thr Ala Thr Ser Ser
 1 5 10 15

Pro Pro Pro Lys Ala Arg Ser Asn Glu Asn Leu Asp Lys Ile Asp Met
 20 25 30

Ser Leu Asp Asp Ile Ile Lys Leu Asn Arg Lys Glu Gly Lys Lys Gln
 35 40 45

Asn Phe Pro Arg Leu Asn Arg Arg Leu Leu Gln Gln Ser Gly Ala Gln
 50 55 60

Gln Phe Arg Met Arg Val Arg Trp Gly Ile Gln Gln Asn Ser Gly Phe
 65 70 75 80

Gly Lys Thr Ser Leu Asn His Arg Gly Arg Val Met Pro Gly Lys Arg
 85 90 95

Arg Pro Asn Gly Val Ile Thr Gly Leu Ala Ala Arg Lys Thr Thr Gly
 100 105 110

Ile Arg Lys Gly Ile Ser Pro Met Asn Arg Pro Pro Leu Ser Asp Lys
 115 120 125

Asn Ile Glu Gln Tyr Phe Pro Val Leu Lys Arg Lys Ala Asn Leu Leu
 130 135 140

177

Arg Gln Asn Glu Gly Gln Arg Lys Pro Val Ala Val Leu Lys Arg Pro
 145 150 155 160

Ser Gln Leu Ser Arg Lys Asn Asn Ile Pro Ala Asn Phe Thr Arg Ser
 165 170 175

Gly Asn Lys Leu Asn His Gln Lys Asp Thr Arg Gln Ala Thr Phe Leu
 180 185 190

Phe Arg Arg Gly Leu Lys Val Gln Ala Gln Leu Asn Thr Glu Gln Leu
 195 200 205

Leu Asp Asp Val Val Ala Lys Arg Thr Arg Gln Trp Arg Thr Ser Thr
 210 215 220

Thr Asn Gly Gly Ile Leu Thr Val Ser Ile Asp Asn Pro Gly Ala Val
 225 230 235 240

Gln Cys Pro Val Thr Gln Lys Pro Arg Leu Thr Arg Thr Ala Val Pro
 245 250 255

Ser Phe Leu Thr Lys Arg Glu Gln Ser Asp Val Lys Lys Val Pro Lys
 260 265 270

Gly Val Pro Leu Gln Phe Asp Ile Asn Ser Val Gly Lys Gln Thr Gly
 275 280 285

Met Thr Leu Asn Glu Arg Phe Gly Ile Leu Lys Glu Gln Arg Ala Thr
 290 295 300

Leu Thr Tyr Asn Lys Gly Gly Ser Arg Phe Val Thr Val Gly
 305 310 315

<210> 201
 <211> 102
 <212> PRT
 <213> Homo sapien

<400> 201

Met Ile Lys Lys Arg Leu Ile Gly Ile Phe Val Asn Phe Arg Lys Gly
 1 5 10 15

Ile Phe Val Asn Leu Tyr Gly Gln Ser Ile Thr Thr Asn Lys His Thr
 20 25 30

178

Asn Thr Gln Gln Arg Thr Ala Phe Gly Glu Lys Pro His Gly Ala Lys
 35 40 45

Glu Arg Lys Gly Pro Pro Gly Gly Glu Thr Ser Gly Asp Thr Thr Pro
 50 55 60

Gly Thr Asn Asn His His Gln Gln Lys Leu Ser Ala Lys Gln Thr Lys
 65 70 75 80

Lys Asn Lys Thr Gln Thr Lys Asn Lys Arg Thr Arg Asn Glu Asp Thr
 85 90 95

Lys Lys Asn Asn Lys Gln
 100

<210> 202
 <211> 107
 <212> PRT
 <213> Homo sapien

<400> 202

Met Glu Thr Gln Pro Leu Leu Leu Tyr Leu Thr Leu Gly Ser Tyr Leu
 1 5 10 15

Phe Phe Leu Ser Pro Gln Ile Phe Leu Ser Leu Leu Glu Trp Asp Leu
 20 25 30

Cys His Leu Arg Gly Cys Ser Ala Tyr Arg Gly Trp Ala Ala Thr Glu
 35 40 45

Val Glu Leu Leu Arg Pro Arg Leu Arg Gly Leu Val Ala Arg Gln Pro
 50 55 60

Cys Thr Ile Phe Phe Ser Thr Pro Ser Leu Val Phe Asn Ser Leu Val
 65 70 75 80

Gly Gly Leu Ala Ala Pro Ser Phe Ile Arg Arg Glu Ala Asn Gly Arg
 85 90 95

Gly Pro Gly Gln Trp Arg Val Val Pro His Lys
 100 105

<210> 203
 <211> 93
 <212> PRT
 <213> Homo sapien

179

<400> 203

Met Cys His Ile Gly Pro Leu Pro Ala Val Ala Lys Ala Ser Cys Phe
1 5 10 15

Ser Pro Thr Glu Glu Thr Val Leu Cys His Asp Asp Arg Ala Leu Leu
20 25 30

Gly Leu Val Phe Leu Val Phe Pro Phe Trp Gln Cys Gly Leu Gln Glu
35 40 45

Leu Asp Val Tyr Ala Gln Gly Ile Glu Phe Thr Leu Lys Leu Gly Asn
50 55 60

Gly Val Phe Asn Leu Cys Ser Cys Leu Phe Ile Leu Leu Phe Ile Phe
65 70 75 80

Cys His Pro Ala Leu Tyr Trp Ala Asn Asn Glu Ile Lys
85 90

<210> 204

<211> 54

<212> PRT

<213> Homo sapien

<400> 204

Met Val Pro Ile Leu Gly Gly Gly Gly Lys Leu Ser Val Arg Leu Phe
1 5 10 15

Gln Cys Gly Asn Thr Lys Tyr Asp Thr Arg Val Ile Ala Met Met Pro
20 25 30

Gly Gly Thr Arg Pro Glu Ala Val Phe Ser Cys Phe Ser Leu Leu Ser
35 40 45

Gly Ile Thr Thr Glu Leu
50

<210> 205

<211> 82

<212> PRT

<213> Homo sapien

<400> 205

Met Thr Phe Ser Met Val His Asp Leu Leu Arg Ala Asp Ala Asn Ser
1 5 10 15

180

Gly Lys Leu Phe Phe Met Ile Ser Lys Asp Leu Gly Tyr Val Asn Glu
 20 25 30

Met Ile Lys Arg His Phe Ser Glu Phe Ala Arg Arg Arg Leu Lys Asn
 35 40 45

Gln Asn Lys Asp Pro Thr Ala Phe His Val Ala Thr Cys Ser Pro Leu
 50 55 60

His His Asn Ser Lys Pro Thr Gly Glu Leu Ser Leu Lys Tyr Thr Phe
 65 70 75 80

Gln Met

<210> 206
 <211> 116
 <212> PRT
 <213> Homo sapien

<400> 206

Leu Tyr Ile Ile Ser Leu Ile Tyr Phe Asn Met Asp Phe Leu Phe Leu
 1 5 10 15

Phe Ser Ala Asp Gly Val Leu Val Cys His Pro Gly Trp Ser Ala Val
 20 25 30

Ala Arg Ser Arg Leu Thr Thr Thr Ser Ala Ser Gln Val Gln Ala Ile
 35 40 45

Leu Leu Ala Ser Ala Ser Gln Phe Thr Gly Ile Thr Gly Thr Cys His
 50 55 60

His Ala Gln Leu Ile Phe Val Phe Leu Val Glu Met Gly Phe His His
 65 70 75 80

Val Asp Gln Ala Asp Phe Glu Leu Leu Thr Ser Gly Asp Ser Pro Ala
 85 90 95

Ser Pro Ser His Ser Ala Gly Ile Ile Gly Met Ser His Cys Pro Arg
 100 105 110

Pro Asp Phe Phe
 115

181

<210> 207
<211> 52
<212> PRT
<213> Homo sapien

<400> 207

Met Ile Ile Ser Lys Met Ser Thr Pro Leu Pro Lys Lys Leu Leu Lys
1 5 10 15

Tyr Leu Tyr Leu Cys Asn Gly Thr His Asp Ser His Gly Pro Arg Ile
20 25 30

Lys Ser Gln Phe Ile Leu Arg Ile Asn Leu Ser Lys Asn Met Ser Ser
35 40 45

Asn Ser His Lys
50

<210> 208
<211> 54
<212> PRT
<213> Homo sapien

<400> 208

Met Ala Leu Ser Leu Tyr Cys Phe Phe Asn Lys Asn Phe Phe Ser Ile
1 5 10 15

Ile Leu Leu Gln Cys Tyr Ser Glu Gln Val Leu Cys Gln Ile Ser Cys
20 25 30

Ile Met Phe Val Trp Lys Ile Lys Phe Tyr Ser Cys Met Val Arg Leu
35 40 45

Phe Gln Leu Leu Ile Leu
50

<210> 209
<211> 82
<212> PRT
<213> Homo sapien

<400> 209

Met Ser Arg Leu Met Leu Tyr Gly Cys Leu Pro Met Ser Gly Ile Val
1 5 10 15

182

Ser Arg Tyr Pro Ser Pro Cys Val Pro Arg Glu Leu Trp Gly Asn Trp
 20 25 30

Ser Pro Glu Lys Pro Thr Cys His Thr His Gly Lys His Pro Met Cys
 35 40 45

His Trp Ser Thr Pro Gln Ala Cys Tyr Val Phe Ile Ile Phe Asp Val
 50 55 60

Phe Met Phe Phe Leu Leu Leu Ile Leu Lys Glu Asn Thr Leu Leu Phe
 65 70 75 80

Ser Asn

<210> 210
 <211> 59
 <212> PRT
 <213> Homo sapien

<400> 210

Met Glu Pro Ser Asp Leu Lys Ser Arg Gln Lys Ser Leu Leu Arg Pro
 1 5 10 15

Val Leu Ala His Pro Ser Pro Arg Thr Cys Gln Ile Arg Cys Ile Arg
 20 25 30

Gln Val Glu Thr Leu Pro Val Asn Ser Gly His Lys Gln Gly Glu Gly
 35 40 45

Arg Thr Asn Gln Pro Pro Ser Ser Tyr Leu Tyr
 50 55

<210> 211
 <211> 112
 <212> PRT
 <213> Homo sapien

<400> 211

Met Gly Ile Ile Leu Asn Trp Leu Asn Gln Trp Ala Gln Ile Thr Tyr
 1 5 10 15

Leu Pro Ser Leu Leu Cys Asp Ser Pro Ala Val Thr His Thr Ile His
 20 25 30

Ile Leu Cys Thr Ser Asn Glu Gln Thr Trp Phe Pro Cys Phe Leu Asp

183

35

40

45

Ile Ser Met Thr Val Ser His Thr Asn Tyr Trp Val Arg Phe Phe Ser
 50 55 60

Cys Tyr Arg Pro Thr Ser Cys Cys Leu Cys Val Val Leu Gln Lys Leu
 65 70 75 80

Ser Ile Pro Thr Pro Leu Leu Cys His Leu Gln Glu Ser Gly Ile Val
 85 90 95

Arg Ser Gln Leu Arg Lys Val Leu Val Pro Leu Thr Gly His Ile Leu
 100 105 110

<210> 212
 <211> 56
 <212> PRT
 <213> Homo sapien

<400> 212

Met Pro Pro Arg Gly Ser Gln Ala Val Ser Ser Ser Gly Arg Ala Ile
 1 5 10 15

Asn Leu Ser Ser Gly Gln Glu Lys Thr Asp His Trp Ser Pro Lys Met
 20 25 30

Leu Asp Ser Ile Ala Arg Ser His Leu Asn Asn Ser Asp Cys Ser Phe
 35 40 45

Thr Gln Val Val Val Gln Asn Leu
 50 55

<210> 213
 <211> 118
 <212> PRT
 <213> Homo sapien

<400> 213

Glu Arg Gln Gly Thr Leu Ser Thr Ala Ala Pro Thr Thr Ser Pro Ala
 1 5 10 15

Pro Cys Leu Ser Asn His His Asn Lys Lys His Leu Ile Leu Ala Phe
 20 25 30

Cys Ala Gly Val Leu Leu Thr Leu Leu Leu Ile Ala Phe Ile Phe Leu
 35 40 45

184

Ile Ile Lys Ser Tyr Arg Lys Tyr His Ser Lys Pro Gln Ala Pro Asp
 50 55 60

Pro His Ser Asp Pro Pro Ala Lys Leu Ser Ser Ile Pro Gly Glu Ser
 65 70 75 80

Leu Thr Tyr Ala Ser Thr Thr Phe Lys Leu Ser Glu Glu Lys Ser Asn
 85 90 95

His Leu Ala Glu Asn His Ser Ala Asp Phe Asp Pro Ile Val Tyr Ala
 100 105 110

Gln Ile Lys Val Thr Asn
 115

<210> 214
 <211> 51
 <212> PRT
 <213> Homo sapien

<400> 214

Met Ala Leu Glu Phe Lys Phe Cys Arg Lys Trp Ile Ala Ile Asn Asn
 1 5 10 15

Pro Met Lys Met Gly His Ile Leu Pro Leu Ile Glu Ser Gln Ser Thr
 20 25 30

Arg Thr Asn Arg Ile Ser His Leu Ser Ile Phe Arg Tyr Gly Arg Gln
 35 40 45

Gln Lys Gln
 50

<210> 215
 <211> 55
 <212> PRT
 <213> Homo sapien

<400> 215

Met Thr Cys Phe Arg Glu Cys Leu Leu Val Tyr Leu Tyr Ser Ile Cys
 1 5 10 15

Leu Leu Asn Ser Leu His Lys Leu Glu Leu Leu Ser Arg Arg Leu Arg
 20 25 30

185

Glu Cys Lys Tyr Val Thr His Lys Met His Trp Ser Met Val Asn Lys
 35 40 45

Thr Asn His Phe Gly Leu Val
 50 55

<210> 216
 <211> 129
 <212> PRT
 <213> Homo sapien

<400> 216

Met Val Ser Arg Pro His Asn Pro Pro Lys Lys Tyr Ala Ala Ser Lys .
 1 5 10 15

Thr Cys Cys Asp Asp Glu Ala Arg Thr Ser Thr Thr Thr Arg Arg His
 20 25 30

Glu Ala Pro Gln Asn Gly Glu Arg Arg Lys Thr Arg Thr Arg Lys Thr
 35 40 45

Arg Asn Glu Glu Thr Glu Arg Thr Pro His Arg Arg Gln Thr Arg Asp
 50 55 60

Arg Lys Lys Gln Glu Thr Met Val Pro His Arg Ala Glu Thr Arg Ser
 65 70 75 80

Ala Ala Gln Arg Glu Gln Ser Thr Glu Ala Asn Ser Arg Ser Thr Gln
 85 90 95

Ser Lys Ala Pro Gln Leu Arg Thr Pro Thr Thr Gln Glu Ala Glu Arg
 100 105 110

Glu Ser Asn Thr His Thr His Ala Thr Gln Ala Thr Glu Arg Arg Thr
 115 120 125

Arg

<210> 217
 <211> 58
 <212> PRT
 <213> Homo sapien

<400> 217

186

Met Gly Ala Asn Pro Pro Phe His Pro Gly Ser Pro Leu Val Pro Pro
 1 5 10 15

Arg Val Ser Pro Gln Leu Ser Phe Phe Phe Cys Phe Val Phe Phe Pro
 20 25 30

Phe Val Phe Phe Phe Cys Phe Phe Arg Phe Phe Ile Ile Leu Phe Thr
 35 40 45

Arg Tyr Thr Gly Leu Lys Lys Ile Ile Ser
 50 55

<210> 218

<211> 116

<212> PRT

<213> Homo sapien

<400> 218

Met Thr Gln Leu Arg His Gln Gln Lys Lys Lys Lys Lys Ala Gly Arg
 1 5 10 15

Thr Gln Gly Gln Ser Gly Ser Arg Cys Arg Met Val Ile Pro Pro Thr
 20 25 30

Phe Pro His Asn Thr Ala Thr Thr Thr His Thr His His His His Thr
 35 40 45

Ala His Pro Ser Ala His Thr His Thr Thr Asn Arg Ser Ala Gly Arg
 50 55 60

Asp Arg Pro Arg Lys Gln Thr Glu Pro Ala Gln Thr Ser Lys His His
 65 70 75 80

Thr Asn Gly Gln His Asp Thr Thr Ala Gln Gly Thr His Lys His Asp
 85 90 95

Ser Thr Trp Pro Thr Pro Pro Pro Arg Ser Tyr Pro His Gly Arg Arg
 100 105 110

Ser Pro Pro Thr
 115

<210> 219

<211> 600

<212> PRT

<213> Homo sapien

187

<400> 219

Met Gly Lys Lys Leu Asp Leu Ser Lys Leu Thr Asp Glu Glu Ala Gln
 1 5 10 15

His Val Leu Glu Val Val Gln Arg Asp Phe Asp Leu Arg Arg Lys Glu
 20 25 30

Glu Glu Arg Leu Glu Ala Leu Lys Gly Lys Ile Lys Lys Glu Ser Ser
 35 40 45

Lys Arg Glu Leu Leu Ser Asp Thr Ala His Leu Asn Glu Thr His Cys
 50 55 60

Ala Arg Cys Leu Gln Pro Tyr Gln Leu Leu Val Asn Ser Lys Arg Gln
 65 70 75 80

Cys Leu Glu Cys Gly Leu Phe Thr Cys Lys Ser Cys Gly Arg Val His
 85 90 95

Pro Glu Glu Gln Gly Trp Ile Cys Asp Pro Cys His Leu Ala Arg Val
 100 105 110

Val Lys Ile Gly Ser Leu Glu Trp Tyr Tyr Glu His Val Lys Ala Arg
 115 120 125

Phe Lys Arg Phe Gly Ser Ala Lys Val Ile Arg Ser Leu His Gly Arg
 130 135 140

Leu Gln Gly Gly Ala Gly Pro Glu Leu Ile Ser Glu Glu Arg Ser Gly
 145 150 155 160

Asp Ser Asp Gln Thr Asp Glu Asp Gly Glu Pro Gly Ser Glu Ala Gln
 165 170 175

Ala Gln Ala Gln Pro Phe Gly Ser Lys Lys Lys Arg Leu Leu Ser Val
 180 185 190

His Asp Phe Asp Phe Glu Gly Asp Ser Asp Asp Ser Thr Gln Pro Gln
 195 200 205

Gly His Ser Leu His Leu Ser Ser Val Pro Glu Ala Arg Asp Ser Pro
 210 215 220

188

Gln Ser Leu Thr Asp Glu Ser Cys Ser Glu Lys Ala Ala Pro His Lys
 225 230 235 240

Ala Glu Gly Leu Glu Glu Ala Asp Thr Gly Ala Ser Gly Cys His Ser
 245 250 255

His Pro Glu Glu Gln Pro Thr Ser Ile Ser Pro Ser Arg His Gly Ala
 260 265 270

Leu Ala Glu Leu Cys Pro Pro Gly Gly Ser His Arg Met Ala Leu Gly
 275 280 285

Thr Ala Ala Ala Leu Gly Ser Asn Val Ile Arg Asn Glu Gln Leu Pro
 290 295 300

Leu Gln Tyr Leu Ala Asp Val Asp Thr Ser Asp Glu Glu Ser Ile Arg
 305 310 315 320

Ala His Val Met Ala Ser His His Ser Lys Arg Arg Gly Arg Ala Ser
 325 330 335

Ser Glu Ser Gln Ile Phe Glu Leu Asn Lys Arg Ile Ser Ala Val Glu
 340 345 350

Cys Leu Leu Thr Tyr Leu Glu Asn Thr Val Val Pro Pro Leu Ala Lys
 355 360 365

Gly Leu Gly Ala Gly Val Arg Thr Glu Ala Asp Val Glu Glu Glu Ala
 370 375 380

Leu Arg Arg Lys Leu Glu Glu Leu Thr Ser Asn Val Ser Asp Gln Glu
 385 390 395 400

Thr Ser Ser Glu Glu Glu Glu Ala Lys Asp Glu Lys Ala Glu Pro Asn
 405 410 415

Arg Asp Lys Ser Val Gly Pro Leu Pro Gln Ala Asp Pro Glu Val Gly
 420 425 430

Thr Ala Ala His Gln Thr Asn Arg Gln Glu Lys Ser Pro Gln Asp Pro
 435 440 445

Gly Asp Pro Val Gln Tyr Asn Arg Thr Thr Asp Glu Glu Leu Ser Glu
 450 455 460

189

Leu Glu Asp Arg Val Ala Val Thr Ala Ser Glu Val Gln Gln Ala Glu
 465 470 475 480

Ser Glu Val Ser Asp Ile Glu Ser Arg Ile Ala Ala Leu Arg Ala Ala
 485 490 495

Gly Leu Thr Val Lys Pro Ser Gly Lys Pro Arg Arg Lys Ser Asn Leu
 500 505 510

Pro Ile Phe Leu Pro Arg Val Ala Gly Lys Leu Gly Lys Arg Pro Glu
 515 520 525

Asp Pro Asn Ala Asp Pro Ser Ser Glu Ala Lys Ala Met Ala Val Pro
 530 535 540

Tyr Leu Leu Arg Arg Lys Phe Ser Asn Ser Leu Lys Ser Gln Gly Lys
 545 550 555 560

Asp Asp Asp Ser Phe Asp Arg Lys Ser Val Tyr Arg Gly Ser Leu Thr
 565 570 575

Gln Arg Asn Pro Asn Ala Arg Lys Gly Met Ala Ser His Thr Phe Ala
 580 585 590

Lys Pro Val Val Ala His Gln Ser
 595 600

<210> 220
 <211> 48
 <212> PRT
 <213> Homo sapien

<400> 220

Met Met Ile Leu Ser Gln Lys Gly Leu Phe Thr Val Tyr Val Asp Ile
 1 5 10 15

Lys Leu Thr Val Cys Ile Tyr Lys Cys Arg Cys Ala Glu Ala Ile Tyr
 20 25 30

Thr Lys Thr Gly Ile Leu Thr Ser Asp Arg Tyr Val Arg Asn Ala Glu
 35 40 45

<210> 221
 <211> 58
 <212> PRT

190

<213> Homo sapien

<400> 221

Met Val Ile Phe Tyr Ser Ser Pro Ser Gln Asp Ser Ala Leu Ile Tyr
1 5 10 15

Tyr Ile Pro Phe Ile Leu Leu Tyr Arg Leu Leu Ser Glu Thr His Val
20 25 30

Gln Ile Arg Asp Lys Ile Leu Lys His Ile Thr Pro Ser Leu Val Phe
35 40 45

Ser Ile Gln Ile Leu Arg Asn Ser Cys Tyr
50 55

<210> 222

<211> 38

<212> PRT

<213> Homo sapien

<400> 222

Met Arg Met Leu Arg Glu Ile Val Gly Cys Leu Glu Phe His Tyr Ile
1 5 10 15

Phe Cys Phe Tyr Phe Leu Ile Pro Arg Cys Phe Phe Lys Ile Phe Arg
20 25 30

Gln Ile Ser Ile Leu His
35

<210> 223

<211> 61

<212> PRT

<213> Homo sapien

<400> 223

Met Trp Cys Lys Lys Val Asp Glu Glu Lys Arg Gly Leu Ser Ser Leu
1 5 10 15

Ala Leu Pro Arg Glu Gly His Gly Gln Arg Leu Thr Asn Thr Cys Pro
20 25 30

Ser Leu Gln Gly Val Ala Gly Phe Gln Asn Lys Ala Phe Arg Ile Lys
35 40 45

Pro Phe Leu Ala Cys Leu Val Leu Gly Met Phe Pro Pro

191

50

55

60

<210> 224
<211> 41
<212> PRT
<213> Homo sapien

<400> 224

Met Ser Leu Phe Val Thr His Asn Val Leu Tyr Arg Lys Leu Leu Leu
1 5 10 15

Ser Tyr Val Ile Leu Ala Val Asp Val Thr Ala Cys His Gln Val Gln
20 25 30

Tyr Val Ile Cys Ile Ser Leu Phe Ser
35 40

<210> 225
<211> 318
<212> PRT
<213> Homo sapien

<400> 225

Met Glu Ala Leu Ala Leu Val Gly Ala Trp Tyr Thr Ala Arg Lys Ser
1 5 10 15

Ile Thr Val Ile Cys Asp Phe Tyr Ser Leu Ile Arg Leu His Phe Ile
20 25 30

Pro Arg Leu Gly Ser Arg Ala Asp Leu Ile Lys Gln Tyr Gly Arg Trp
35 40 45

Ala Val Val Ser Gly Ala Thr Asp Gly Ile Gly Lys Ala Tyr Ala Glu
50 55 60

Glu Leu Ala Ser Arg Gly Leu Asn Ile Ile Leu Ile Ser Arg Asn Glu
65 70 75 80

Glu Lys Leu Gln Val Val Ala Lys Asp Ile Ala Asp Thr Tyr Lys Val
85 90 95

Glu Thr Asp Ile Ile Val Ala Asp Phe Ser Ser Gly Arg Glu Ile Tyr
100 105 110

Leu Pro Ile Arg Glu Ala Leu Lys Asp Lys Asp Val Gly Ile Leu Val
115 120 125

192

Asn Asn Val Gly Val Phe Tyr Pro Tyr Pro Gln Tyr Phe Thr Gln Leu
 130 135 140

Ser Glu Asp Lys Leu Trp Asp Ile Ile Asn Val Asn Ile Ala Ala Ala
 145 150 155 160

Ser Leu Met Val His Val Val Leu Pro Gly Met Val Glu Arg Lys Lys
 165 170 175

Gly Ala Ile Val Thr Ile Ser Ser Gly Ser Cys Cys Lys Pro Thr Pro
 180 185 190

Gln Leu Ala Ala Phe Ser Ala Ser Lys Ala Tyr Leu Asp His Phe Ser
 195 200 205

Arg Ala Leu Gln Tyr Glu Tyr Ala Ser Lys Gly Ile Phe Val Gln Ser
 210 215 220

Leu Ile Pro Phe Tyr Val Ala Thr Ser Met Thr Ala Pro Ser Asn Phe
 225 230 235 240

Leu His Arg Cys Ser Trp Leu Val Pro Ser Pro Lys Val Tyr Ala His
 245 250 255

His Ala Val Ser Thr Leu Gly Ile Ser Lys Arg Thr Thr Gly Tyr Trp
 260 265 270

Ser His Ser Ile Gln Phe Leu Phe Ala Gln Tyr Met Pro Glu Trp Leu
 275 280 285

Trp Val Trp Gly Ala Asn Ile Leu Asn Arg Ser Leu Arg Lys Glu Ala
 290 295 300

Leu Ser Cys Thr Ala Arg Lys Glu Ala Leu Ser Cys Thr Ala
 305 310 315

<210> 226

<211> 37

<212> PRT

<213> Homo sapien

<400> 226

Met Ala Gly Ser Gly Lys Val Pro Ile Thr Thr Thr Tyr Lys Pro Pro
 1 5 10 15

193

Thr Asn Ser Asn Ala Ile His Leu Pro Thr Pro Ile Ile Arg Lys Ala
 20 25 30

Gly Phe Thr Gly Ile
 35

<210> 227
 <211> 87
 <212> PRT
 <213> Homo sapien

<400> 227

Met Phe Leu Phe Leu Phe Phe Val Val Ser Ser Cys Ser Ala Leu Leu
 1 5 10 15

Ser Pro Ser Phe Leu Ser Arg Pro Pro Pro Leu Ala Val Gly Gly Arg
 20 25 30

Arg Val Cys Gly Trp Gly Asn Cys Val Arg Arg Ala Arg Asp His Asn
 35 40 45

Cys Pro Pro Pro Arg Gly Pro Gln Arg Leu Thr Thr Pro Thr Arg Tyr
 50 55 60

Thr Pro Arg Val Leu Phe Phe Phe Leu Phe Leu Phe Tyr Phe Leu Phe
 65 70 75 80

Cys Phe Val Val Gly Lys Met
 85

<210> 228
 <211> 30
 <212> PRT
 <213> Homo sapien

<400> 228

Met Asn Ser Phe Gly Tyr Met Thr Pro Ser Lys Phe Phe Lys Lys Glu
 1 5 10 15

Ile Thr Phe Lys Thr Thr Tyr Ile Phe Cys Phe Cys Leu Arg
 20 25 30

<210> 229
 <211> 52
 <212> PRT

194

<213> Homo sapien

<400> 229

Met Arg Gly Val His Lys Ser Thr Gln Thr Ile Ala Glu Cys Val Gly
 1 5 10 15

Val Asn Arg Ser Pro Met Phe Leu Tyr Ser Gly Ile Tyr Ile Tyr Thr
 20 25 30

Phe Thr Gln Thr Asn Lys Ser Ser Ile Leu Gln Thr Pro Phe Gly Thr
 35 40 45

Arg Asp Pro Lys
 50

<210> 230

<211> 125

<212> PRT

<213> Homo sapien

<400> 230

Met Arg Ala Leu Arg Phe His Leu Thr Gly Asp Glu Met Ala Ala Ala
 1 5 10 15

Asp Ile Leu Pro Cys Leu Gln Ala Leu Leu Ala Leu Pro Ala Leu Pro
 20 25 30

Ser Leu Gln Thr Pro Thr Ala Val Ala Leu Pro Leu Arg Lys Leu Ser
 35 40 45

Asp Cys Ile Ile Pro Arg Pro Arg Arg Leu Cys Ser Ala Leu Leu Met
 50 55 60

Ala Val Ile Pro Arg Glu Arg Gln Glu Pro Gly Ala Ser Gly Met Gln
 65 70 75 80

Pro Leu Gly Tyr Ser Val Cys Phe Gln Leu Cys Leu Cys Phe Ser Arg
 85 90 95

Val Phe Leu Arg Gln Leu Thr Gln Tyr Leu Ser Thr Leu Ser Leu Gly
 100 105 110

Pro Ala Leu Gly Arg Ile Phe Phe Tyr Phe Val Lys Val
 115 120 125

195

<210> 231
 <211> 273
 <212> PRT
 <213> Homo sapien

<400> 231

Arg Gly Pro Ala Arg Ser Ala Ala Pro Ala Gly Gly Ser Ser Ser Gly
 1 5 10 15

Cys Gly Ala Ala Pro Gly Ala Gly Gly Gly Arg Arg Pro Gly His Gly
 20 25 30

Arg Pro Val Gly Pro Gly Thr Ala Ala Gly Ala Ala Gly Pro Gly Leu
 35 40 45

Pro Ala Arg Thr His His Arg His His Pro Gly Cys Leu Pro Gln Gln
 50 55 60

Ala Ala Pro Pro Ala Gly Arg Gly Pro Ala Ala Arg Arg Gly Ala Ala
 65 70 75 80

Ala Gly Gly Gly Pro Ala Ala Gly Arg Gly Ala Val Thr Gly Arg Gly
 85 90 95

Pro Val Thr Arg Gly Cys Ala Ala Ala Arg Pro Ala Arg Arg Gly Leu
 100 105 110

Ser Ala Gly Gly Ala Leu Ala Leu Pro Ala Gly Leu Gly Leu Gly Leu
 115 120 125

Arg Asp Pro Gly Ala Tyr Gly Asp Ile Arg Pro Ser Ala Ala Ser Trp
 130 135 140

Val Gly Ser Arg Gly Leu Ala Tyr Pro Pro Ala Arg Arg Asn Ser Gly
 145 150 155 160

Ala Ala Pro Arg Ser Gly Ala Ala Pro Gly Gly Arg Gly Arg Pro Asp
 165 170 175

Ala Arg Gln Gly His Ala Gly Pro Gly Ser Arg Gly Pro Pro Leu Val
 180 185 190

Gly Ser Val Ser Arg Pro Gly Ala Ala Ala Phe Leu Pro Pro Arg Ser
 195 200 205

196

Arg Pro Ala Pro Gly Pro Ala Gly Asp Ser Ser Gly Pro Cys Trp Arg
 210 215 220

Gly Glu Gly Pro Ala Ala Gly Gly Ala Pro Ala Gly Ala Leu Ala Leu
 225 230 235 240

Ser Ala Ser Ala Leu Gly Gln Pro Arg Ala Thr Ala Arg Leu Pro Gly
 245 250 255

His Pro Leu Gly Glu Asp Gly Gln Ala Leu Ser Ala Ala Gly Gly Gly
 260 265 270

Gly

<210> 232
 <211> 104
 <212> PRT
 <213> Homo sapien

<400> 232

Met Pro Ser Phe Phe Cys Phe Ser Ile Ser Leu Ile Arg Asp Trp Lys
 1 5 10 15

Val Ser Ile Arg Ser Asn Thr Asp Phe Ile Val Ile Gly Thr Asn Cys
 20 25 30

Ser Pro Thr Thr Pro Tyr Ser Ala Ser Ser Ile Thr Leu Leu Cys Glu
 35 40 45

Ile Leu Arg Asn Gly Leu Pro Leu Gln Gly Leu Asn Leu Pro Tyr Leu
 50 55 60

Arg Phe Glu Ser Ser Val Leu Phe Cys Ile Cys Phe Lys Tyr Leu Gly
 65 70 75 80

Ser Val Thr His Ala Asn Met Thr Cys Pro Val Gln Ala Thr Leu Gly
 85 90 95

Ile His Ile Ser His Val Ser Ser
 100

<210> 233
 <211> 260
 <212> PRT
 <213> Homo sapien

197

<400> 233

Glu Lys Lys Lys Lys Met Lys Asn Glu Asn Ala Asp Lys Leu Leu Lys
 1 5 10 15

Ser Glu Lys Gln Met Lys Lys Ser Glu Lys Lys Ser Lys Gln Glu Lys
 20 25 30

Glu Lys Ser Lys Lys Lys Lys Gly Gly Lys Thr Glu Gln Asp Gly Tyr
 35 40 45

Gln Lys Pro Thr Asn Lys His Phe Thr Gln Ser Pro Lys Lys Ser Val
 50 55 60

Ala Asp Leu Leu Gly Ser Phe Glu Gly Lys Arg Arg Leu Leu Leu Ile
 65 70 75 80

Thr Ala Pro Lys Ala Glu Asn Asn Met Tyr Val Gln Gln Arg Asp Glu
 85 90 95

Tyr Leu Glu Ser Phe Cys Lys Met Ala Thr Arg Lys Ile Ser Val Ile
 100 105 110

Thr Ile Phe Gly Pro Val Asn Asn Ser Thr Met Lys Ile Asp His Phe
 115 120 125

Gln Leu Asp Asn Glu Lys Pro Met Arg Val Val Asp Asp Glu Asp Leu
 130 135 140

Val Asp Gln Arg Leu Ile Ser Glu Leu Arg Lys Glu Tyr Gly Met Thr
 145 150 155 160

Tyr Asn Asp Phe Phe Met Val Leu Thr Asp Val Asp Leu Arg Val Lys
 165 170 175

Gln Tyr Tyr Glu Val Pro Ile Thr Met Lys Ser Val Phe Asp Leu Ile
 180 185 190

Asp Thr Phe Gln Ser Arg Ile Lys Asp Met Glu Lys Gln Lys Lys Glu
 195 200 205

Gly Ile Val Cys Lys Glu Asp Lys Lys Gln Ser Leu Glu Asn Phe Leu
 210 215 220

198

Ser Arg Phe Arg Trp Arg Arg Arg Leu Leu Val Ile Ser Ala Pro Asn
 225 230 235 240

Asp Glu Asp Trp Ala Tyr Ser Gln Gln Leu Ser Ala Leu Ser Gly Gln
 245 250 255

Ala Cys Thr Leu
 260

<210> 234
 <211> 72
 <212> PRT
 <213> Homo sapien

<400> 234

Met Glu Gly Glu Lys Gly Gln Glu Pro Gln Lys Leu Arg Asn Gly Leu
 1 5 10 15

Ala Leu Pro Leu Phe Arg Pro His Ile Ala Asp Arg Trp Ala Ala Glu
 20 25 30

Thr Ser Thr Ile Gly His Asn Asn Asp Asn Asn Tyr Ser Thr Thr Phe
 35 40 45

Tyr Phe Phe Ile Glu Tyr Gln Gly Leu Gln Ser Ala Phe Thr Leu Ile
 50 55 60

Ile Leu Trp Val Gly Thr Cys Pro
 65 70

<210> 235
 <211> 52
 <212> PRT
 <213> Homo sapien

<400> 235

Met Thr Leu Phe Ile Arg Cys Cys Thr Asn Tyr Gly Asn Leu Cys Gln
 1 5 10 15

Tyr Phe Asn Val Cys Trp Ile Ile Thr Asp Ile Phe Ile Ile Leu Met
 20 25 30

Ser Thr Asn Leu Phe Ile Leu Ile Ala Arg Val Ser Leu Gly Ser Lys
 35 40 45

His His Leu Gly

199

50

<210> 236
 <211> 75
 <212> PRT
 <213> Homo sapien

<400> 236

Met Phe Leu Cys Tyr Phe Ser Gly Leu Ile Phe Leu Phe Ile Phe Pro
 1 5 10 15

Val Cys Leu Trp Gln His Leu Ser Ile Leu Tyr Leu Leu Val Asn Leu
 20 25 30

Leu Phe Thr Leu Ile Leu Arg Ala Ser Tyr Pro Ser His Cys Ala Ala
 35 40 45

Arg Gln His Leu Glu Gln His Cys Pro Ile Val Ser Ile Met Pro Glu
 50 55 60

Tyr Gly Trp Gly Gly Arg Cys Phe Gly Trp Leu
 65 70 75

<210> 237
 <211> 75
 <212> PRT
 <213> Homo sapien

<400> 237

Met Ala Tyr Arg Met Lys Arg Gly Thr Arg Asn Pro Cys Gly Arg Gly
 1 5 10 15

Leu Asp Leu Lys Gln Cys Pro Leu Trp Leu Leu Leu Pro Trp Leu Thr
 20 25 30

Gly Phe Leu Asp His Val His Phe Thr Gly Pro Trp Asp Leu His Leu
 35 40 45

Leu Ala Ser Pro Ala Gly Leu Ile Pro Ala Arg Ala Pro Ser Phe Leu
 50 55 60

Leu Met Val Phe Arg Trp Pro Asp His Gly Lys
 65 70 75

<210> 238
 <211> 212

200

<212> PRT

<213> Homo sapien

<400> 238

Ser Pro His Gln Ala Ala Ala Pro Val Asp Gln Thr Pro Arg Thr Leu
 1 5 10 15

Ala Thr Met Gly Gln Arg Ala Leu Pro Ser Ser Leu Ala Leu Leu Ser
 20 25 30

Arg Pro Leu Ser Pro Pro Pro Ala Ala Cys Ser Gly Asp Pro Gly Cys
 35 40 45

Gly Ser Gly Ala Gly Leu Pro Ser Ala Ser Ala Ala Ala Gly Ile Ala
 50 55 60

Ser Ser Ala Val Glu Pro Val Cys Gly Asp Ala Ala Pro Ala Cys Leu
 65 70 75 80

Leu Arg Thr Pro Leu Arg Gly Leu Leu Lys Pro Thr Gly Pro Arg Ser
 85 90 95

Thr Met Glu Cys Pro Pro Ala Leu Ile Val His Pro Pro Ala Gly Gly
 100 105 110

Met Ala Ser Gly Ser Ser Gln Pro Trp Ala Ala Ala Ser Ala Thr Pro
 115 120 125

Met Leu Ser Ser Lys Ala Ser Leu Cys Ile Pro Thr Arg Gly Pro Pro
 130 135 140

Pro Gln Pro Leu Met Arg Thr Pro Ala Ala Arg Ser His Trp Pro Ile
 145 150 155 160

Pro His Pro Cys Asp Thr Ala Cys Pro Ala Pro Leu Pro Val Val Leu
 165 170 175

Val Ala Pro Arg Ser Thr Ile Leu Ser Met Ser Arg Thr Trp Thr Cys
 180 185 190

Arg Arg Trp Ala Val Ala Pro Cys Arg Ala Glu Lys Leu Met Cys Ser
 195 200 205

Ser Ser Arg Ser
 210

201

<210> 239
 <211> 62
 <212> PRT
 <213> Homo sapien

<400> 239

Met Asn Phe Thr Leu Ala Ile Phe His Tyr Phe Ser Leu Ser Gln Met
 1 5 10 15

Ser Val Leu Met Arg Gln Leu Ala Leu Thr Gly Ala Thr Leu Met Cys
 20 25 30

His Leu Pro Thr Phe Asn Phe Trp Val Lys Ala Glu Arg Glu Lys Leu
 35 40 45

Met Asp Phe Ser Phe Ser Arg Arg Asp Lys Asn Gln Leu His
 50 55 60

<210> 240
 <211> 128
 <212> PRT
 <213> Homo sapien

<400> 240

Cys Leu Ile Ser Ala Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
 1 5 10 15

Lys Lys Lys Asn Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
 20 25 30

Lys Lys Thr Lys Lys Arg Arg Gly Gly Gly Arg Glu Lys Glu Pro Arg
 35 40 45

Gly Glu His Arg Ala Gly Arg Arg Ala His Met Lys Lys Ala Thr Gln
 50 55 60

Lys Lys Lys His Lys Thr Ser Lys Arg Lys Gln Lys Lys Ala Glu Arg
 65 70 75 80

Glu Lys Val Thr Arg Arg Ile Glu Arg Lys Ala Leu Gln Asp Gln His
 85 90 95

Gly Thr Asn Gln Lys Gln Ile Asn Lys Glu Asn Lys Thr Asp Thr Arg
 100 105 110

202

Cys Gln Arg Ala Asn Ala Arg Thr Met Glu Thr Gly Lys Gln His Lys
 115 120 125

<210> 241
 <211> 41
 <212> PRT
 <213> Homo sapien
 <400> 241

Met Leu Leu Glu Arg Arg Ser Val Met Asp Ala Trp Ser Arg Arg Gly
 1 5 10 15

Thr Phe Ser Lys Ile Ser Met Gln Leu Phe Asn Arg Glu Ser Arg Phe
 20 25 30

His Gln Asp Ser Asn Gln Ser Asn Ile
 35 40

<210> 242
 <211> 42
 <212> PRT
 <213> Homo sapien
 <400> 242

Met Pro Tyr Phe Trp Arg Lys Val Gly Asn Ile Gly Val Ser Leu Ser
 1 5 10 15

Val Ser Gln Glu Asp Ser Phe Val Leu Leu Gly Glu Pro Val Pro Tyr
 20 25 30

Arg Phe Val Tyr Thr Val Ile Ile Gln Asp
 35 40

<210> 243
 <211> 45
 <212> PRT
 <213> Homo sapien
 <400> 243

Met Glu Pro His Ile Met Lys Phe Asn Ser His Val Lys Thr Phe Cys
 1 5 10 15

Ile Val Gly Cys Gln Lys Tyr Phe Pro Asn Phe Arg Leu Thr Cys Arg
 20 25 30

Ala Gly Asp Gly Leu Pro Pro Tyr Asn Phe Lys Ser Val

203

35

40

45

<210> 244
 <211> 785
 <212> PRT
 <213> Homo sapien

<400> 244

Lys Ala Lys Ile Ser Trp Glu Ala Pro Val Glu Lys Lys Thr Glu Cys
 1 5 10 15

Ile Gln Lys Gly Lys Asn Asn Gln Val Gly Ala Trp Thr Leu Leu Leu
 20 25 30

Val Leu Pro Ser Pro Gln Asp Val Ser Ser His Ser Gly Pro Arg Ala
 35 40 45

Leu Thr Asn Arg Thr Pro Phe Cys Pro Gln Thr Glu Cys Phe Asn Phe
 50 55 60

Ile Arg Phe Leu Gln Pro Tyr Asn Ala Ser His Leu Tyr Val Cys Gly
 65 70 75 80

Thr Tyr Ala Phe Gln Pro Lys Cys Thr Tyr Val Asn Met Leu Thr Phe
 85 90 95

Thr Leu Glu His Gly Glu Phe Glu Asp Gly Lys Gly Lys Cys Pro Tyr
 100 105 110

Asp Pro Ala Lys Gly His Ala Gly Leu Leu Val Asp Gly Glu Leu Tyr
 115 120 125

Ser Ala Thr Leu Asn Asn Phe Leu Gly Thr Glu Pro Ile Ile Leu Arg
 130 135 140

Asn Met Gly Pro His His Ser Met Lys Thr Glu Tyr Leu Ala Phe Trp
 145 150 155 160

Leu Asn Glu Pro His Phe Val Gly Ser Ala Tyr Val Pro Glu Ser Val
 165 170 175

Gly Ser Phe Thr Gly Asp Asp Asp Lys Val Tyr Phe Phe Phe Arg Glu
 180 185 190

Arg Ala Val Glu Ser Asp Cys Tyr Ala Glu Gln Val Val Ala Arg Val

204

195	200	205
Ala Arg Val Cys Lys Gly Asp Met Gly Gly Ala Arg Thr Leu Gln Arg		
210	215	220
Lys Trp Thr Thr Phe Leu Lys Ala Arg Leu Ala Cys Ser Ala Pro Asn		
225	230	235 240
Trp Gln Leu Tyr Phe Asn Gln Leu Gln Ala Met His Thr Leu Gln Asp		
	245	250 255
Thr Ser Trp His Asn Thr Thr Phe Phe Gly Val Phe Gln Ala Gln Trp		
	260	265 270
Gly Asp Met Tyr Leu Ser Ala Ile Cys Glu Tyr Gln Leu Glu Glu Ile		
	275	280 285
Gln Arg Val Phe Glu Gly Pro Tyr Lys Glu Tyr His Glu Glu Ala Gln		
	290	295 300
Lys Trp Asp Arg Tyr Thr Asp Pro Val Pro Ser Pro Arg Pro Gly Ser		
305	310	315 320
Cys Ile Asn Asn Trp His Arg Arg His Gly Tyr Thr Ser Ser Leu Glu		
	325	330 335
Leu Pro Asp Asn Ile Leu Asn Phe Val Lys Lys His Pro Leu Met Glu		
	340	345 350
Glu Gln Val Gly Pro Arg Trp Ser Arg Pro Leu Leu Val Lys Lys Gly		
	355	360 365
Thr Asn Phe Thr His Leu Val Ala Asp Arg Val Thr Gly Leu Asp Gly		
	370	375 380
Ala Thr Tyr Thr Val Leu Phe Ile Gly Thr Gly Asp Gly Trp Leu Leu		
385	390	395 400
Lys Ala Val Ser Leu Gly Pro Trp Val His Leu Ile Glu Glu Leu Gln		
	405	410 415
Leu Phe Asp Gln Glu Pro Met Arg Ser Leu Val Leu Ser Gln Ser Lys		
	420	425 430

205

Val Lys Leu Leu Phe Ala Gly Ser Arg Ser Gln Leu Val Gln Leu Pro
 435 440 445

Val Ala Asp Cys Met Lys Tyr Arg Ser Cys Ala Asp Cys Val Leu Ala
 450 455 460

Arg Asp Pro Tyr Cys Ala Trp Ser Val Asn Thr Ser Arg Cys Val Ala
 465 470 475 480

Val Gly Gly His Ser Gly Ser Leu Leu Ile Gln His Val Met Thr Ser
 485 490 495

Asp Thr Ser Gly Ile Cys Asn Leu Arg Gly Ser Lys Lys Val Arg Pro
 500 505 510

Thr Pro Lys Asn Ile Thr Val Val Ala Gly Thr Asp Leu Val Leu Pro
 515 520 525

Cys His Leu Ser Ser Asn Leu Ala His Ala Arg Trp Thr Phe Gly Gly
 530 535 540

Arg Asp Leu Pro Ala Glu Gln Pro Gly Ser Phe Leu Tyr Asp Ala Arg
 545 550 555 560

Leu Gln Ala Leu Val Val Met Ala Ala Gln Pro Arg His Ala Gly Ala
 565 570 575

Tyr His Cys Phe Ser Glu Glu Gln Gly Ala Arg Leu Ala Ala Glu Gly
 580 585 590

Tyr Leu Val Ala Val Val Ala Gly Pro Ser Val Thr Leu Glu Ala Arg
 595 600 605

Ala Pro Leu Glu Asn Leu Gly Leu Val Trp Leu Ala Val Val Ala Leu
 610 615 620

Gly Ala Val Cys Leu Val Leu Leu Leu Leu Val Leu Ser Leu Arg Arg
 625 630 635 640

Arg Leu Arg Glu Glu Leu Glu Lys Gly Ala Lys Ala Thr Glu Arg Thr
 645 650 655

Leu Val Tyr Pro Leu Glu Leu Pro Lys Glu Pro Thr Ser Pro Pro Phe
 660 665 670

206

Arg Pro Cys Pro Glu Pro Asp Glu Lys Leu Trp Asp Pro Val Gly Tyr
 675 680 685

Tyr Tyr Ser Asp Gly Ser Leu Lys Ile Val Pro Gly His Ala Arg Cys
 690 695 700

Gln Pro Gly Gly Gly Pro Pro Ser Pro Pro Pro Gly Ile Pro Gly Gln
 705 710 715 720

Pro Leu Pro Ser Pro Thr Arg Leu His Leu Gly Gly Gly Arg Asn Ser
 725 730 735

Asn Ala Asn Gly Tyr Val Arg Leu Gln Leu Gly Gly Glu Asp Arg Gly
 740 745 750

Gly Leu Gly His Pro Leu Pro Glu Leu Ala Asp Glu Leu Arg Arg Lys
 755 760 765

Leu Gln Gln Arg Gln Pro Leu Pro Asp Ser Asn Pro Glu Glu Ser Ser
 770 775 780

Val
 785

<210> 245
 <211> 43
 <212> PRT
 <213> Homo sapien

<400> 245

Met Pro Leu Leu Ser Met Arg Gly Thr Gln Pro Glu Thr Gly His Gly
 1 5 10 15

Val Lys Leu Ala Ser Leu Lys Thr Gly Arg Ser Ile Ser Glu Met Asp
 20 25 30

Leu Gly Ser Ala Ile Leu Val Gly Tyr Asn Tyr
 35 40

<210> 246
 <211> 38
 <212> PRT
 <213> Homo sapien

<400> 246

207

Met Ala Gln Ile Val Gly Lys Glu Lys Thr Phe Leu Phe Lys Gln Arg
 1 5 10 15

Lys Gly Phe Gly Glu Lys Thr Gly Ser Gly Ser Gly Glu Val Phe Val
 20 25 30

Met Leu Gly Asp Arg Leu
 35

<210> 247
 <211> 31
 <212> PRT
 <213> Homo sapien

<400> 247

Met Phe Cys Leu Cys Ser Pro Val Leu Cys Tyr Cys Asn Phe Phe Phe
 1 5 10 15

Phe Tyr Thr Lys His Val Thr Trp Thr Asn Val Arg Gln Met Thr
 20 25 30

<210> 248
 <211> 50
 <212> PRT
 <213> Homo sapien

<400> 248

Met Arg Asn Ser Ser Pro Ile Leu Thr Pro Ala Leu Phe Ser Phe His
 1 5 10 15

Met Tyr Ile Gly Pro Leu Ile Arg Ile Phe Lys Lys Phe Pro Arg Pro
 20 25 30

Pro Asn Leu Thr Ile Asp Asp Pro Leu Ser Leu Phe Arg Arg Asn Tyr
 35 40 45

Ile Gly
 50

<210> 249
 <211> 77
 <212> PRT
 <213> Homo sapien

<400> 249

Met Leu Leu Ala Val Arg Thr Thr Val Ile Cys Leu Gln Ser Cys Cys
 1 5 10 15

208

Cys Arg Ile Gln Arg Thr Ala Thr Ile Thr Leu Asn Cys Phe Ala Leu
20 25 30

Ser Ser Ile Phe Asp Tyr Tyr Ile Ser His Asn Ile Thr Ile Ser His
35 40 45

Ser Ser Asn Tyr Ser Ala Gln Ile His Glu His Val Pro Ala Arg Ala
 50 55 60

Ala Ala Arg Ser Ile Thr Trp Arg Arg Ser Ala Cys Ile
65 70 75

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<210> 250
<211> 70
<212> PRT
<213> Homo sapien
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<400> 250

Met Pro Gly Ser His Leu Cys Met Phe Asn Thr Val Thr His Asp Val
1 5 10 15

Ile Thr Glu Trp Arg Arg Trp Lys Gly Pro Cys Arg Ser Phe Ser Trp
20 25 30

His Pro Asn Phe Thr Glu Gly Glu Leu Arg Pro Glu Leu Arg Asp Val
35 40 45

Leu Arg Ile Pro Glu Ser His Ser Ser Val Arg Ser Val Ile His Lys
50 55 60

Glu Val Ile Ile Lys Val
65 70

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<210> 251
<211> 117
<212> PRT
<213> Homo sapien
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<400> 251

Met Gly Thr Ala Lys Lys Lys Lys Gln Thr Glu Arg Gln Thr Arg Gly
1 5 10 15

Ile His Thr Thr Gly Glu Lys Glu Tyr Thr Gln Arg Gly Lys Arg Gly
20 25 30

209

Asn Thr Ala Gln Lys Pro His Arg Gln Ala Gln Gln Asp Arg Ala Thr
 35 40 45

Gly His Asp Ala Thr Arg Thr Arg Pro Arg Ala Leu Trp Asn Gly Ala
 50 55 60

Ala Gly Arg Val Glu Ala Gly Ser Leu His Gln Gly Arg Arg Ala Asp
 65 70 75 80

Trp Arg Gly Gly Gly Glu Ala Gly Asp Arg Asn Arg Glu Arg Glu Gly
 85 90 95

Gly Lys Cys Ala Gly Gly Arg Lys Arg Arg Arg Arg Glu Gly Thr Glu
 100 105 110

Gly Glu Thr Gln Gln
 115

<210> 252
 <211> 66
 <212> PRT
 <213> Homo sapien

<400> 252

Met Val Val Cys Leu Trp Leu Cys Ser Ser Val Ser Leu Ala Leu Cys
 1 5 10 15

Val Ser Phe Val Ala Leu Ser Ser Val Pro Ser Cys Leu Arg Thr Val
 20 25 30

Gly Gly Asp Phe Gly Arg Gly Asn Gln Phe Leu Pro Arg Gly Pro Ala
 35 40 45

Leu Ala Gln Gly Ser Pro Ser Ala Phe Phe Leu Phe Cys Cys Phe Phe
 50 55 60

Phe Phe
 65

<210> 253
 <211> 31
 <212> PRT
 <213> Homo sapien

<400> 253

210

Met Leu Glu Ala Ile Leu Gly Pro Val Ser Asn Ser Leu Tyr Val Ser
 1 5 10 15

Gly Lys Thr Cys His Gly Ser Arg Ser Val Phe Ser Ser Ala Lys
 20 25 30

<210> 254

<211> 37

<212> PRT

<213> Homo sapien

<400> 254

Met Thr Leu Ala Thr Ile Ile His Ser Ile Val Gln Ala Gly Ser Leu
 1 5 10 15

Gly Cys Cys Ile Lys Cys Asn Pro Pro Leu Gly Ile Leu Glu Pro Gln
 20 25 30

Asn Lys His Cys Val
 35

<210> 255

<211> 45

<212> PRT

<213> Homo sapien

<400> 255

Met Tyr Leu Gly Gln Leu Gly Asn His Arg Leu Lys Lys Leu Thr Leu
 1 5 10 15

Val Ile Thr Arg Val Val Ser Asp Tyr Lys Gln His Ile Ile Asn Pro
 20 25 30

Thr Ala Leu Ile Leu Ala Gln Arg Gln Asn Trp Thr Phe
 35 40 45

<210> 256

<211> 32

<212> PRT

<213> Homo sapien

<400> 256

Met Asn His Arg Ile Leu Gln Asn Tyr Ser Leu Phe Ser Lys Met Ile
 1 5 10 15

Asn Glu Leu Gln Ser Leu Pro Ser Arg Ser Ser Gln Leu Asn Lys Gly
 20 25 30

211

<210> 257
 <211> 31
 <212> PRT
 <213> Homo sapien

<400> 257

Met Ile Leu Leu Phe Leu Ser Lys Thr Ser Ser Ser Lys Ile Val Tyr
 1 5 10 15

Met Val Thr Phe Val Ser Asn Asn Val Met Val Asn Ser Gly Tyr
 20 25 30

<210> 258
 <211> 62
 <212> PRT
 <213> Homo sapien

<400> 258

Met Thr Ser Ser Met Leu Lys Ser Glu Ser Ser Ala Ser Ile Phe Val
 1 5 10 15

Ile Pro His Ile Gln Ser Ser Ala Lys Ser Cys Gln Phe Tyr Leu Lys
 20 25 30

Ser Phe Pro Ser Phe Phe Leu Thr Tyr Val Ile Ser Val Val Ser Gln
 35 40 45

Leu His Leu Ser Ser Tyr Ser Ser Leu Leu Tyr Thr Gln Cys
 50 55 60

<210> 259
 <211> 103
 <212> PRT
 <213> Homo sapien

<400> 259

Phe Phe Val Phe Ala Arg Gln Gly Leu Thr Leu Ser Pro Arg Leu Glu
 1 5 10 15

Cys Ser Gly Met Ile Ile Thr His Cys Ser Leu Gln Leu Leu Gly Ser
 20 25 30

Ser Asn Ser Pro Ala Ser Ala Ser Ala Glu Thr Glu Thr Ile Gly Met
 35 40 45

212

Arg His His Ile Trp Leu Thr Phe Gln Leu Ser Val Glu Thr Gly Ser
 50 55 60

Cys Tyr Val Ala Gln Ala Ala Leu Lys Phe Leu Ala Ser Ser Asn Pro
 65 70 75 80

Leu Ala Ser Ala Ser His Ser Thr Gly Ile Thr Gly Met Ser His Pro
 85 90 95

Thr Pro Pro Gln Ser Asp Phe
 100

<210> 260

<211> 42

<212> PRT

<213> Homo sapien .

<400> 260

Met Val Gln Ser Ser Asp His Met Glu Val Gly Lys Arg Glu Leu Ile
 1 5 10 15

Thr Gly Leu Tyr Ala Gly Glu Trp Ile Val Leu Ile Leu Thr Val Ser
 20 25 30

Lys Glu Asn Gln Leu Ser Ser Ser Ser Arg
 35 40

<210> 261

<211> 26

<212> PRT

<213> Homo sapien

<400> 261

Met Thr Cys Phe Lys Leu Leu Phe Tyr Val Leu Leu Tyr Phe Cys Ser
 1 5 10 15

His Leu His Val Ala Lys Gln Ile Met Leu
 20 25

<210> 262

<211> 397

<212> PRT

<213> Homo sapien

<400> 262

Met Glu Gly Asn Arg Asp Glu Ala Glu Lys Cys Val Glu Ile Ala Arg
 1 5 10 15

213

Glu Ala Leu Asn Ala Gly Asn Arg Glu Lys Ala Gln Arg Phe Leu Gln
 20 25 30

Lys Ala Glu Lys Leu Tyr Pro Leu Pro Ser Ala Arg Ala Leu Leu Glu
 35 40 45

Ile Ile Met Lys Asn Gly Ser Thr Ala Gly Asn Ser Pro His Cys Arg
 50 55 60

Lys Pro Ser Gly Ser Gly Asp Gln Ser Lys Pro Asn Cys Thr Lys Asp
 65 70 75 80

Ser Thr Ser Gly Ser Gly Glu Gly Gly Lys Gly Tyr Thr Lys Asp Gln
 85 90 95

Val Asp Gly Val Leu Arg Ala Leu Trp Ile Leu Glu His Ala Tyr Gly
 100 105 110

Met Val Asp Leu Tyr Leu Thr His Thr Thr Asn Lys Cys Lys Asn Tyr
 115 120 125

Tyr Glu Val Asp Gly Val Thr Lys Asp Ala Gly Asp Glu Asp Leu Lys
 130 135 140

Lys Ala Tyr Arg Lys Leu Ala Leu Lys Phe His Pro Asp Lys Asn His
 145 150 155 160

Ala Pro Gly Ala Thr Asp Ala Phe Lys Lys Ile Gly Asn Ala Tyr Ala
 165 170 175

Val Leu Ser Asn Pro Glu Lys Arg Lys Gln Tyr Asp Leu Thr Gly Asn
 180 185 190

Glu Glu Gln Ala Cys Asn His Gln Asn Asn Gly Arg Phe Asn Phe His
 195 200 205

Arg Gly Cys Glu Ala Asp Ile Thr Pro Glu Asp Leu Phe Asn Ile Phe
 210 215 220

Phe Gly Gly Gly Phe Pro Ser Gly Ser Val His Ser Phe Ser Asn Gly
 225 230 235 240

Arg Ala Gly Tyr Ser Gln Gln His Gln His Arg His Ser Gly His Glu

214
 245 250 255
 Arg Glu Glu Glu Arg Gly Asp Gly Gly Phe Ser Val Phe Ile Gln Leu
 260 265 270
 Met Pro Ile Ile Val Leu Ile Leu Val Ser Leu Leu Ser Gln Leu Met
 275 280 285
 Val Ser Asn Pro Pro Tyr Ser Leu Tyr Pro Arg Ser Gly Thr Gly Gln
 290 295 300
 Thr Ile Lys Met Gln Thr Glu Asn Leu Gly Val Val Tyr Tyr Val Asn
 305 310 315 320
 Lys Asp Phe Lys Asn Glu Tyr Lys Gly Met Leu Leu Gln Lys Val Glu
 325 330 335
 Lys Ser Val Glu Glu Asp Tyr Val Thr Asn Ile Arg Asn Asn Cys Trp
 340 345 350
 Lys Glu Arg Gln Gln Lys Thr Asp Met Gln Tyr Ala Ala Lys Val Tyr
 355 360 365
 Arg Asp Asp Arg Leu Arg Arg Lys Ala Asp Ala Leu Ser Met Asp Asn
 370 375 380
 Cys Lys Glu Leu Glu Arg Leu Thr Ser Leu Tyr Lys Gly
 385 390 395
 <210> 263
 <211> 54
 <212> PRT
 <213> Homo sapien
 <400> 263
 Met Cys Phe Gly Cys Arg Lys Thr Cys Lys Thr Ser Asn Asn Pro Tyr
 1 5 10 15
 Phe Pro Thr Leu Arg Gly Trp Phe Ser Arg Val Cys Val Cys Val Cys
 20 25 30
 Val Cys Val Cys Met Asn Asp Ile Phe Ile Thr Leu Phe Arg Lys Arg
 35 40 45
 Met Ser Val Leu Cys Val

215

50

<210> 264
 <211> 31
 <212> PRT
 <213> Homo sapien

<400> 264

Met Lys Gly Asn Gln Phe Ser Val Thr Asp Asp Val Lys Ile Leu Phe
 1 5 10 15

Ser Gly Lys Leu Tyr Ser His Ser Lys Ile Gln Ser Met Leu Leu
 20 25 30

<210> 265
 <211> 219
 <212> PRT
 <213> Homo sapien

<400> 265

Val Ala Met Val Glu Val Gln Leu Glu Ser Asp His Glu Tyr Pro Pro
 1 5 10 15

Gly Leu Leu Val Ala Phe Ser Ala Cys Thr Thr Val Leu Val Ala Val
 20 25 30

His Leu Phe Ala Leu Met Val Ser Thr Cys Leu Leu Pro His Ile Glu
 35 40 45

Ala Val Ser Asn Ile His Asn Leu Asn Ser Val His Gln Ser Pro His
 50 55 60

Gln Arg Leu His Arg Tyr Val Glu Leu Ala Trp Gly Phe Ser Thr Ala
 65 70 75 80

Leu Gly Thr Phe Leu Phe Leu Ala Glu Val Val Leu Val Gly Trp Val
 85 90 95

Lys Phe Val Pro Ile Gly Ala Pro Leu Asp Thr Pro Thr Pro Met Val
 100 105 110

Pro Thr Ser Arg Val Pro Gly Thr Leu Ala Pro Val Ala Thr Ser Leu
 115 120 125

Ser Pro Ala Ser Asn Leu Pro Arg Ser Ser Ala Ser Ala Ala Pro Ser
 130 135 140

216

Gln Ala Glu Pro Ala Cys Pro Pro Arg Gln Ala Cys Gly Gly Gly Gly
 145 150 155 160

Ala His Gly Pro Gly Trp Gln Ala Ala Met Ala Ser Thr Ala Ile Met
 165 170 175

Val Pro Val Gly Leu Val Phe Val Ala Phe Ala Leu His Phe Tyr Arg
 180 185 190

Ser Leu Val Ala His Lys Thr Asp Arg Tyr Lys Gln Glu Leu Glu Glu
 195 200 205

Leu Asn Arg Leu Gln Gly Glu Leu Gln Ala Val
 210 215

<210> 266
 <211> 33
 <212> PRT
 <213> Homo sapien

<400> 266

Met Phe Thr Arg Lys Pro Lys Ser Ser Lys Ala Gln Leu Leu Leu Leu
 1 5 10 15

Arg Thr Leu His Gln Leu Leu Phe Gln Thr Ser Leu Gln Leu Leu Gly
 20 25 30

Leu

<210> 267
 <211> 88
 <212> PRT
 <213> Homo sapien

<400> 267

Gly Arg Val Arg Phe Val Val Glu Leu Ala Asp Pro Lys Leu Glu Val
 1 5 10 15

Lys Trp Tyr Lys Asn Gly Gln Glu Ile Arg Pro Ser Thr Lys Tyr Ile
 20 25 30

Phe Glu His Lys Gly Cys Gln Arg Ile Leu Phe Ile Asn Asn Cys Gln
 35 40 45

217

Met Thr Asp Asp Ser Glu Tyr Tyr Val Thr Ala Gly Asp Ala Lys Cys
50 55 60

Ser Thr Glu Leu Phe Val Arg Glu Pro Pro Phe Met Val Pro Ser Ser
65 70 75 80

Trp Ile Glu Thr Pro Ala Asp Cys
85

<210> 268
<211> 11
<212> PRT
<213> Homo sapien

<400> 268

Met Trp Arg Ala Lys Gln Tyr Asp Leu Gln Thr
1 5 10

<210> 269
<211> 32
<212> PRT
<213> Homo sapien

<400> 269

Met Glu Gln Ile Glu Asp Asn Asp Ile Cys Phe Tyr Tyr Lys Val Phe
1 5 10 15

His His Leu Ile Ser Leu Thr His Ile Met Arg Pro Ala Phe Glu Glu
20 25 30

<210> 270
<211> 19
<212> PRT
<213> Homo sapien

<400> 270

Met His Ile Lys Met His Ser Leu Ser Cys Pro Asn Asn Tyr His Ile
1 5 10 15

Thr Leu Trp

<210> 271
<211> 173
<212> PRT
<213> Homo sapien

218

<400> 271

Met Ile Gly Cys Ser Leu Leu Val Ala Cys Leu Cys Cys Leu Val Gln
 1 5 10 15

Ser Phe Arg Ala Met Phe Ser Cys Phe Ser Gly Leu Ser Leu Cys Leu
 20 25 30

Met Leu Pro Leu Trp Cys Val Cys Pro Thr Val Cys Ala Phe Phe Cys
 35 40 45

Gly Tyr Leu Leu Phe Phe Ser Leu Arg His Ala Ala Cys Gly Cys Leu
 50 55 60

Leu Val Cys Leu Ser Cys Leu Ala Leu Pro Ser Gly Pro Ile Leu Ser
 65 70 75 80

Phe Ser Phe Cys Leu Arg Val Val Ser Ser Val Arg Val Ala Cys Ala
 85 90 95

Arg Ser Ala Ala Val Leu Leu Leu Arg Gly Val Pro Pro Pro Ser Leu
 100 105 110

Arg Thr Leu Ser Leu Ile Ala Ser Thr Ala Thr Arg Leu Ser Phe Val
 115 120 125

Phe Leu Phe Ser Leu Pro Arg Gly Leu Leu Cys Val Gly Gly Ser Gly
 130 135 140

Ser Val Leu Gly Ser Leu Val Arg Arg Ala Gln Ser Val Gly Leu Arg
 145 150 155 160

Asp Phe Val Ser Val Leu Gln Val Val Leu Thr Cys Leu
 165 170

<210> 272

<211> 20

<212> PRT

<213> Homo sapien

<400> 272

Met Ile Gly Ile Thr Trp Cys Phe Glu Leu Ile His Pro Thr Leu Glu
 1 5 10 15

Leu Thr Ala Thr
 20

219

<210> 273
 <211> 85
 <212> PRT
 <213> Homo sapien

<400> 273

Met Ser Ile Tyr Leu Ala Pro Asp Gly Asn Thr Lys Ser Trp Gln Trp
 1 5 10 15

Glu Trp Lys Gly Ser Leu Ser Gln Ile Leu Pro Tyr Tyr Val Asp Pro
 20 25 30

Lys Ala Gly Leu Gly Ser Lys Ala His Lys Pro Pro Lys Gln Ile Phe
 35 40 45

Thr Glu His Leu Asp Tyr Tyr Arg Pro Ser Ile Leu Leu Gly Thr Met
 50 55 60

Gly Asp Val Lys Glu Val Ile Ser His Met Ile Cys Leu Gln Gly Ala
 65 70 75 80

Lys Asn Ala Ser Gly
 85

<210> 274
 <211> 86
 <212> PRT
 <213> Homo sapien

<400> 274

Met Met Asn Phe Leu Cys Leu Asn Phe Arg Asp Ile Trp Cys Asp Phe
 1 5 10 15

His Leu Tyr Leu Met Leu Pro Leu Leu Pro Ser Leu Leu Asn Thr Ser
 20 25 30

Lys Asn Ser Glu His Ile Leu Ile Pro Pro Val Phe Tyr Phe Tyr Asp
 35 40 45

Leu Asp Ile Leu His His Lys Ile Pro Pro Asn Trp Asp Tyr Val Phe
 50 55 60

Glu Val Ile His Phe Thr Ile Ile Thr Thr Ile Thr Ile Ile Phe Ile
 65 70 75 80

220

Val Cys Phe Val Pro Gly
85

<210> 275
<211> 36
<212> PRT
<213> Homo sapien

<400> 275

Met Phe Phe Glu Met Leu Glu Ile Leu Gly Asn Tyr Gln Met Tyr Arg
1 5 10 15

Ser Cys Met Lys Val Ile Glu Arg Cys Asn Cys Leu Leu Thr Ile Thr
20 25 30

Trp Ile Ser Tyr
35

<210> 276
<211> 35
<212> PRT
<213> Homo sapien

<400> 276

Met Ala Gln Thr Ser Ala Thr Ile Thr His Asn Asn Ser Thr Ala Phe
1 5 10 15

Ile Phe Gly Ser Asn Val Met Gln Val Asn Leu Leu Met Ile Ser Lys
20 25 30

Ile Thr Lys
35

<210> 277
<211> 105
<212> PRT
<213> Homo sapien

<400> 277

Met Ala Thr Gly Thr Pro Glu Ser Gln Ala Arg Phe Gly Gln Ser Val
1 5 10 15

Lys Gly Leu Leu Thr Glu Lys Val Thr Thr Cys Gly Thr Asp Val Ile
20 25 30

Ala Leu Thr Lys Gln Val Leu Lys Gly Ser Arg Ser Ser Glu Leu Leu

221

35

40

45

Gly Gln Ala Ala Arg Asn Met Val Leu Gln Glu Asp Ala Ile Leu His
 50 55 60

Ser Glu Asp Ser Leu Arg Lys Met Ala Ile Ile Thr Thr His Leu Gln
 65 70 75 80

Tyr Gln Gln Glu Ala Ile Gln Lys Asn Val Glu Gln Ser Ser Asp Leu
 85 90 95

Gln Asp Gln Leu Asn His Leu Leu Lys
 100 105

<210> 278
 <211> 41
 <212> PRT
 <213> Homo sapien

<400> 278

Met Lys His Pro Leu Leu Thr Ala Pro Met Gln Asn Ser Thr Ile Gln
 1 5 10 15

Leu Thr Ala Phe Thr Leu Met Thr Arg Cys Lys Ser Lys His Lys Thr
 20 25 30

Glu Asn Met Tyr Val Pro Ala Arg Ala
 35 40

<210> 279
 <211> 35
 <212> PRT
 <213> Homo sapien

<400> 279

Met Phe Arg Glu Ile Val Pro Ile Ser Gln Gly Gly Gln Leu Asp Ser
 1 5 10 15

Asn Gly Val Lys Thr His Leu Lys Val Tyr Cys Lys Asn Ile Tyr Ser
 20 25 30

Pro Lys Leu
 35

<210> 280
 <211> 83

222

<212> PRT

<213> Homo sapien

<400> 280

Met Ser Met Ile Tyr Thr Leu Val Tyr Lys Ala Val Tyr Ile Val Leu
1 5 10 15

Val Leu Asp Leu Leu Val Ser Leu Leu Gly Glu Phe Gly Arg Glu Thr
20 25 30

Leu Pro Pro Gly Pro Leu Gly Pro Gly Gly Ala Pro Ala Phe Phe Phe
35 40 45

Cys Phe Phe Phe Val Phe Val Asn Asn Lys Ile His Leu Leu Lys Glu
50 55 60

Ser Cys Leu His Arg Tyr Arg Thr Ser Trp Ile Phe Gln His His Ser
65 70 75 80

Asn Thr Asn

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ning of each regular issue of the PCT Gazette.*

(54) Title: COMPOSITIONS AND METHODS RELATING TO BREAST SPECIFIC GENES AND PROTEINS

(57) Abstract: The present invention relates to newly identified nucleic acids and polypeptides present in normal and neoplastic breast cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions comprising the nucleic acids, polypeptides, antibodies, variants, derivatives, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and non-cancerous disease states in breast tissue, identifying breast tissue, monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered breast tissue for treatment and research.

WO 2002/077232 A3

INTERNATIONAL SEARCH REPORT

Intern .pplication No
PCT/US 01/43815

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/47 G01N33/50 C12N15/62 C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EMBL, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! 29 September 2000 (2000-09-29) SUGANO S ET AL: "Homo sapiens cDNA: FLJ23313 fis, clone HEP11919" Database accession no. AK026966 XP002230460 the whole document	1,2,4,5
X	DATABASE EMBL 'Online! 22 April 1995 (1995-04-22) BOUILLAUD F: "Clontech adult human fat cell library HL1108A Homo sapiens cDNA clone 20k15" Database accession no. R17114 XP002230461 the whole document	1,2,4,5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

10 February 2003

Date of mailing of the international search report

13.06.03

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Espen, J

INTERNATIONAL SEARCH REPORT

Internat^l Application No
PCT/US 01/43815

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 00 08210 A (RECIPON HERVE ; DIADEXUS LLC (US); SUN YONGMING (US); CAFFERKEY ROB) 17 February 2000 (2000-02-17) -----</p>	

INTERNATIONAL SEARCH REPORT

In international application No.
PCT/US 01/43815

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-17 (in part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claim :

Invention 1; Claims: in part: 1-17; all as far as applicable

Polynucleotide relating to SEQ ID NO 1. Method for determining the presence of a breast specific nucleic acid (BSNA). Polypeptide encoded by said polynucleotide. Antibody binding to said polypeptide. Methode of determining the presence of a breast specific protein in a sample. Method of diagnosing and monitoring the presence of breast cancer in patient. Vaccine comprising said polypeptide or said nucleic acid.

Inventions 2-164; Claims: in part: 1-17; all as far as applicable

as invention 1 but limited to subject-matter relating to SEQ ID NOs 2-164; wherein
invention 2 is limited to SEQ ID NO 2
invention 3 is limited to SEQ ID NO 3, etc ...
invention 164 is limited to SEQ ID NO 164.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter

Application No

PCT/US 01/43815

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0008210	A	17-02-2000	CA 2347906 A1
			EP 1105528 A1
			JP 2002522751 T
			WO 0008210 A1
			17-02-2000
			13-06-2001
			23-07-2002
			17-02-2000